THE REACTION OF HYDRAZOIC ACID WITH ALDEHYDES AND EPOXIDES

by

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INTRODUCTION AND HISTORICAL REVIEW

A. THE REACTION OF HYDRAZOIC ACID WITH ORGANIC COMPOUNDS

Hydrazoic acid, HN_3, is a colorless liquid, b. p. 37°, miscible with water and alcohol, and very soluble in other organic solvents. It is extremely toxic, concentrations in the air of 0.3 to 3.9 parts per million causing a rapid and severe fall in both diastolic and systolic blood pressure, with headaches. (1) The central nervous system is affected, toxic effects including depression of the vaso-motor center and respiratory paralysis. (2)

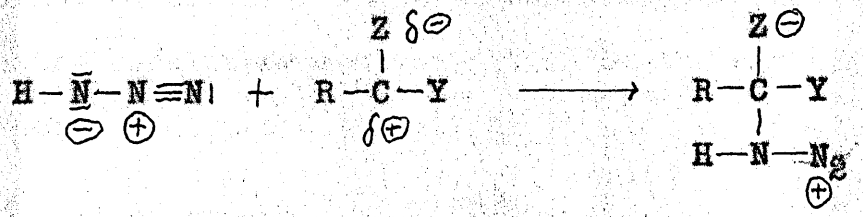
The structure of the azide ion was studied by Hendricks and Pauling. (3) With the aid of the theory of space groups, they interpreted data obtained from Laue and spectral photographs of sodium and potassium azide crystals; and showed the azide ion to possess, not a ring structure, but a linear arrangement of the three nitrogen atoms. In order to determine the structure of organic azides, Brockway and Pauling (4) studied the electron diffraction pattern of gaseous methyl azide and found the result to be compatible only with a linear resonance hybrid such as:

$$H_3C-\underset{\ominus}{\overline{N}}-\underset{\oplus}{N}\equiv N| \quad \longleftrightarrow \quad H_3C-\underset{\oplus}{N}=N=\underset{\ominus}{N}|$$

Therefore it is reasonable to conclude that hydrazoic acid itself has a similar structure:

$$\text{I} \qquad H-\underset{\ominus}{\overline{N}}-\underset{\oplus}{N}\equiv N| \quad \longleftrightarrow \quad H-\underset{\oplus}{N}=N=\underset{\ominus}{N}| \qquad \text{II}$$

Its reactions are the result of its interaction with an electrophilic center in another molecule:



This addition complex may then cyclize directly, or it may rearrange with expulsion of nitrogen, or it may rearrange after first being dehydrated. These and other possibilities for the reaction of this complex will be illustrated in the following discussion.

Hydrazoic acid has been shown to undergo reactions with a great variety of functional groups in organic compounds.

Schmidt (5,6) found that hydrazoic acid decomposes in the presence of concentrated sulfuric acid at temperatures above 30°, with the formation of hydroxylamine, water, and sulfur dioxide. He explained this by assuming that the first step in the reaction is the decomposition of the hydrazoic acid into nitrogen and an imide radical, HN. This then is partly oxidized by the sulfuric acid to form sulfur dioxide and more nitrogen. The water formed by the reduction of the sulfuric acid reacts with part of the imide radical to form hydroxylamine.

In the presence of benzene, aniline and hydrazine are formed. The formation of aniline is explained by the attack of the radical on the benzene ring. The hydrazine results from dimerization of the radical with subsequent disproportionation:

$$2\ HN{=}NH \longrightarrow H_2N\text{-}NH_2 + N_2$$

The mechanism for the formation of aniline in this reaction was supported by the work of Keller and Smith, (7) who gave the following reasons for accepting it:

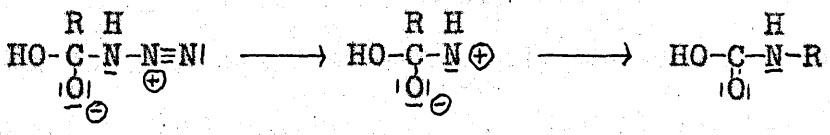
1. The decomposition of hydrazoic acid is unimolecular, the rate determining step probably being the decomposition into nitrogen and the HN radical.
2. Aromatic nuclei are aminated only under conditions such that the decomposition of hydrazoic acid is proceeding actively.
3. The imide radical by itself, when generated photochemically from hydrazoic acid, is capable of aminating toluene.
4. The amination of aromatic nuclei is always accompanied by the formation of one or more of the decomposition products of the imide radical, namely: ammonia, hydrazine, and hydroxylamine.
5. The amination of aromatic nuclei proceeds according to the usual orientation rules when it is carried out on toluene, chlorobenzene and nitrobenzene. Since these

rules apply to reactions which are generally accepted as being reactions of cationoid groups with aromatic nuclei, the attacking group in the hydrazoic acid amination must therefore be a cationoid group. The HN radical, with its open sextet of electrons, can be considered a cationoid group.

The reaction of carboxylic acids with hydrazoic acid in the presence of an acid catalyst to give amines, nitrogen and carbon dioxide was also discovered by Schmidt. (8) It has since become a well known and widely used method for converting carboxylic acids to amines. (10) The most commonly used catalyst is concentrated sulfuric acid. However a wide variety of protonic and non-protonic acid catalysts have been used, such as hydrogen chloride, anhydrous stannic chloride, and ferric chloride. Smith (21) arranged the following catalysts in this increasing order of strength: aqueous hydrochloric acid, hydrogen chloride in dioxane, molten trichloracetic acid, concentrated sulfuric acid. He suggested that highest yields are obtained when the catalyst used is only as strong as necessary to bring about reaction, but no stronger.

Schmidt (6) proposed that the imino radical was also an intermediate in the reactions of hydrazoic acid with carbonyl compounds. Briggs and Lyttleton (9) showed

that this suggestion was incorrect. Schmidt himself reported that the decomposition of hydrazoic acid proceeds at a reasonable rate only at temperatures above 50°. When even easily substituted aromatic compounds, such as anisole and dimethylaniline, were submitted to the conditions of the Schmidt reaction at 40°, no amines could be isolated. On the other hand, almost all acids will undergo the reaction at this temperature. Later Newman and Gildenhorn (11) showed that some acids underwent the reaction even at 0°. Accordingly, Briggs and Lyttleton proposed a new mechanism for the reaction of hydrazoic acid with carboxylic acids. They proposed that the two reacting molecules are activated by the sulfuric acid; and that these activated forms combine to give the intermediate III. This loses nitrogen, and the ion IV thus formed rearranges to give a carbamic acid V, which easily decarboxylates to form the amine.



III IV V

They also carried out a quantitative study on the influence exerted by substituents in the reaction of aromatic acids with hydrazoic acid under standard conditions. The time of half reaction with respect to

nitrogen evolution was considered to be a measure of the speed of the reaction. The speed of reaction diminished in the following order:

m-methylbenzoic acid

benzoic acid

m-ethoxybenzoic acid

m-methoxybenzoic acid

m-hydroxybenzoic acid

m-bromobenzoic acid

m-chlorobenzoic acid

m-iodobenzoic acid

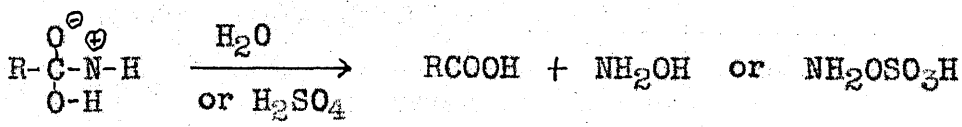
m-carboxybenzoic acid (isophthalic acid)

m-cyanobenzoic acid

m-nitrobenzoic acid

The strengths of these acids are nearly in reverse order. Therefore it appears that nucleophilic substituents in the ring increase the speed of the reaction.

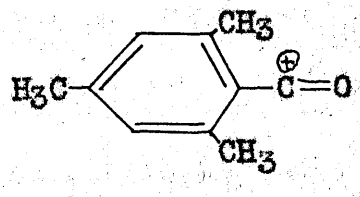
Briggs and Lyttleton observed that often a 100% yield of nitrogen was obtained, but still some of the starting acid was recovered. To account for this, they proposed, without supporting experimental evidence, the following alternative route of decomposition of IV:



IV

Since this decomposition would be influenced by the electrophilic nature of R, the amount of the decomposition which took place would be dependent on the nature of the starting acid, as they in fact found.

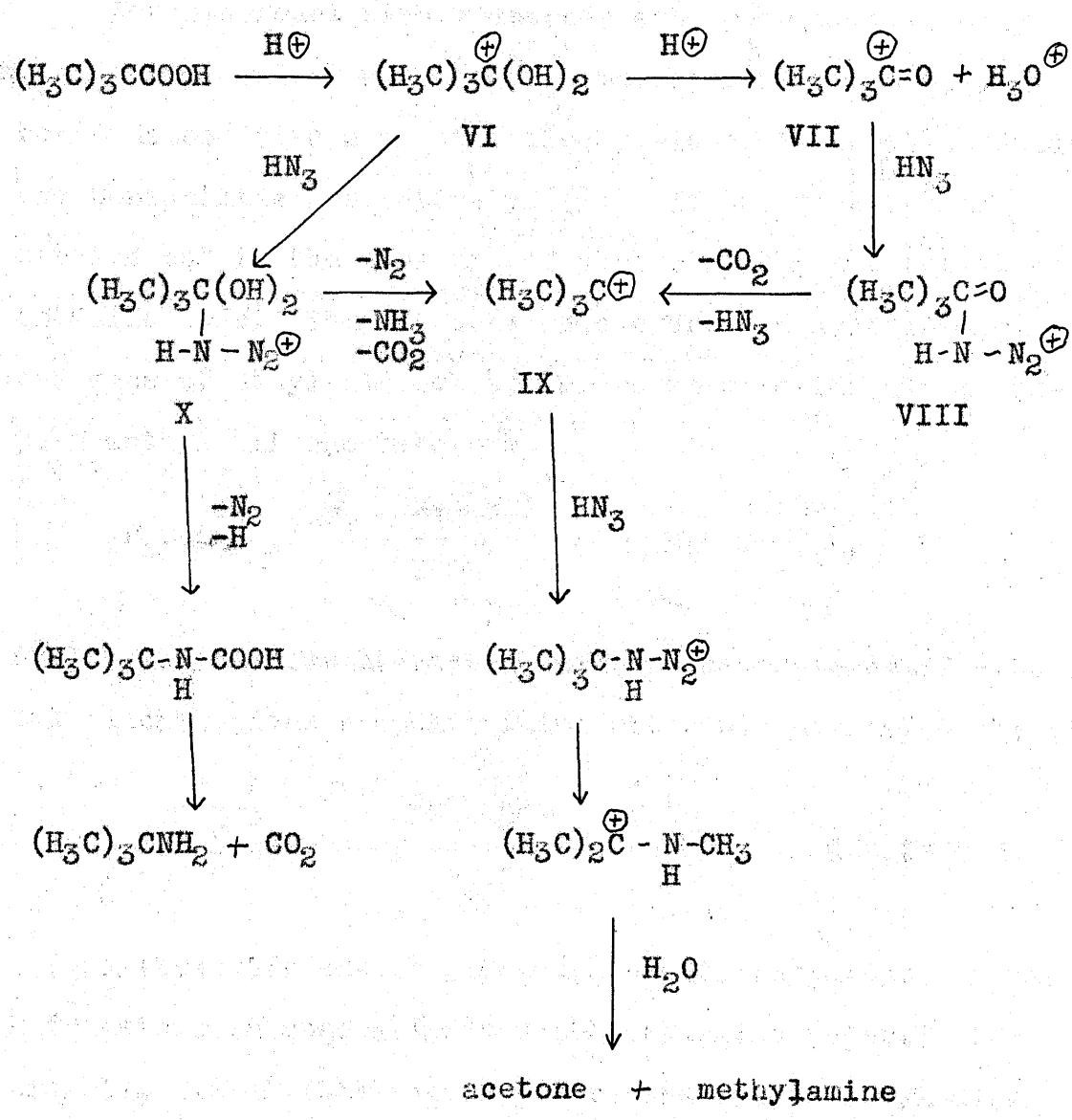
Newman and Gildenhorn (11) went further in describing the nature of the catalytic action of the acid. Since most acids dissolved in sulfuric acid give an i value of two as determined by the freezing point depression of the solution, they proposed that the acid actually reacts in the form of an ion. Indeed, formation of such an ion would be expected to increase the electrophilic nature of the carbon atom involved in the primary reaction with the hydrazoic acid molecule. Furthermore they found that, whereas unhindered acids require a temperature of 40° or more, 2,4,6-trimethylbenzoic acid reacts with hydrazoic acid in sulfuric acid at 0°. Since this acid has been shown to give an i value of four in sulfuric acid, it is probable that the reactive ion in the case of this acid is, not the dihydroxymesitylmethyl carbonium ion, but the oxomesitylmethyl carbonium ion:



When 2,6-dimethylterephthalic acid was treated with hydrazoic acid under the usual conditions the only product

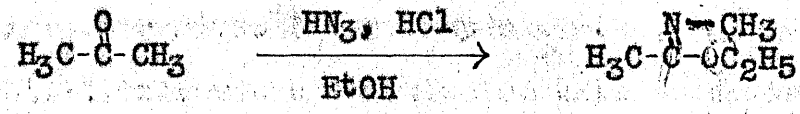
was 4-amino-3,5-dimethylbenzoic acid. These facts show that acids capable of forming an oxo-carbonium ion react at a lower temperature and react faster at any given temperature than those which are capable of forming only dihydroxy-carbonium ions. The higher temperature required for the reaction of unhindered acids may be due to the need to produce more oxocarbonium ions or to the lower reactivity of the dihydroxy-carbonium ion.

Schuerch and Huntress (12) found that trimethylacetic acid on reaction with hydrazoic acid gave not only tertiary butylamine and carbon dioxide but also ammonia, methylamine, acetone, and carbon monoxide. The formation of carbon monoxide could be avoided by dilution of the reaction medium with nitromethane, but the cleavage products still formed. These authors believed the carbon monoxide was the result of the decomposition of the ion VIII formed from the oxo-carbonium ion VII and hydrazoic acid. In addition to carbon monoxide, a tertiary carbonium ion IX would be formed from this decomposition. This carbonium ion could react with hydrazoic acid to form the methylamine and acetone. Since the formation of carbon monoxide could be suppressed without suppressing the formation of the cleavage products, an alternate route to the carbonium ion had to be assumed. Schuerch and Huntress suggested the decomposition of the ion X as such a route. The whole process can be represented as follows:

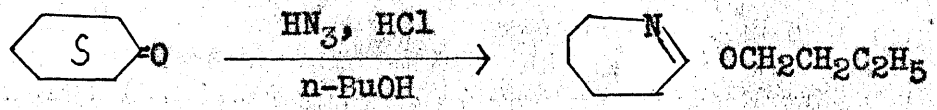


Acid anhydrides, acid chlorides, (8) and esters (13) yield the same amines as the acids from which they are derived. The only lactones which have been subjected to the Schmidt reaction are phthalide and phenolphthalein; and both are unreactive. Phthalimide is also unreactive. (14)

Ketones react with hydrazoic acid much more readily than acids, and at much lower temperatures. Acetone and benzophenone give a quantitative yield of N-methylacetamide and benzanilide respectively. (15) If the reaction is carried out in the presence of alcohols, the product is an iminoester. Thus acetone plus hydrazoic acid in the presence of ethyl alcohol and hydrogen chloride gives ethyl N-methyl iminoacetate:



Cyclohexanone plus hydrazoic acid in the presence of n-butyl alcohol gives a cyclic imino ester of butyl alcohol: (16)



Acetoacetic esters give alpha-acetamino acids. Beta-keto esters in general give alpha-acylamino esters. For example, 2,2-dimethyl-acetoacetic ester gives ethyl alpha-acetamino-isobutyric acid. 2-Carbethoxycyclohexanone gives the lactam of alpha-aminoadipic acid. (17)

Schmidt proposed as the mechanism of the reaction of ketones the addition of the imino radical to the carbonyl group to give an oxime, which then underwent the Beckmann rearrangement. (6) This mechanism is unacceptable for reasons previously discussed; and because some oximes are unaffected by sulfuric acid. For example the oxime of alpha-

hydrindone is unchanged by sulfuric acid even at 100°, whereas in the Schmidt reaction alpha-hydrindone is smoothly converted into dihydrocarbostyril at 40°. (22)

Smith and coworkers (18-21) studied the reaction of a great variety of unsymmetrical ketones with hydrazoic acid. With most of the ketones the product consists of a mixture of two amides. The results they obtained are summarized in Table I. It will be seen from these results that the intrinsic migratory aptitude of the groups concerned has very little if anything to do with determining to what extent the groups migrate in this reaction. With this in mind, Smith proposed the following mechanism for the reaction: (21)

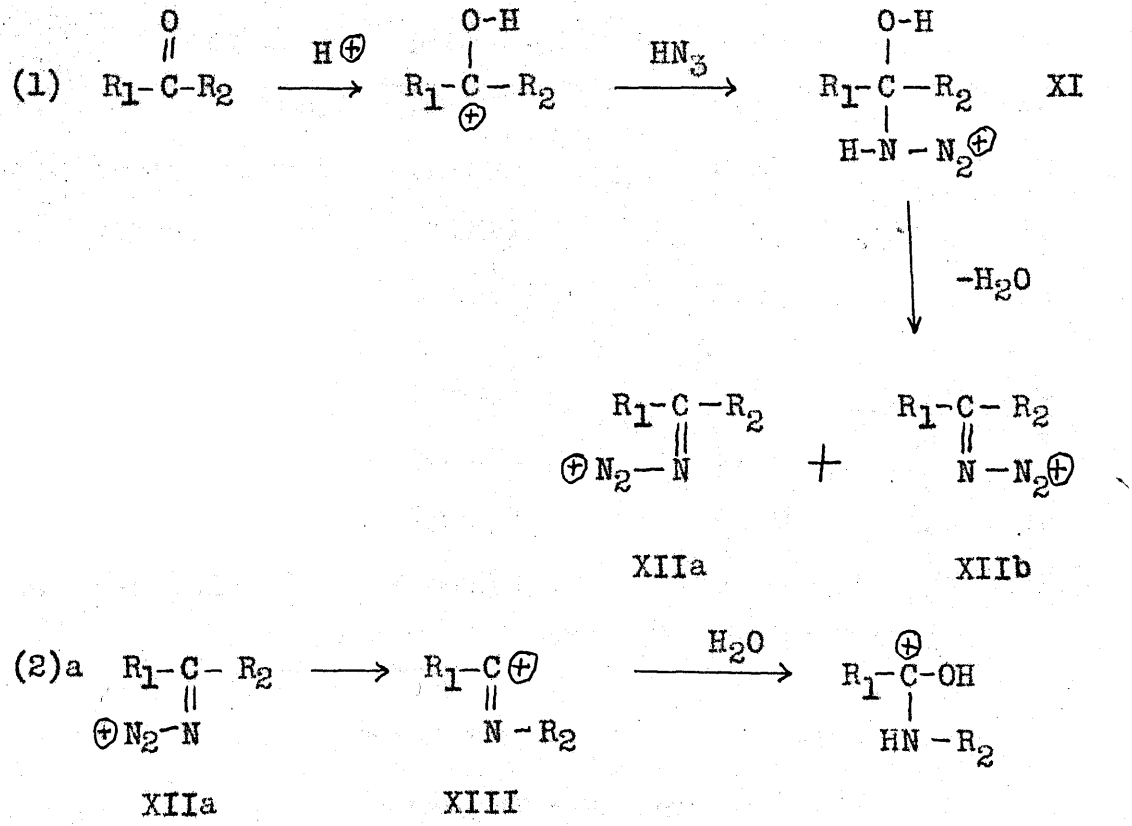
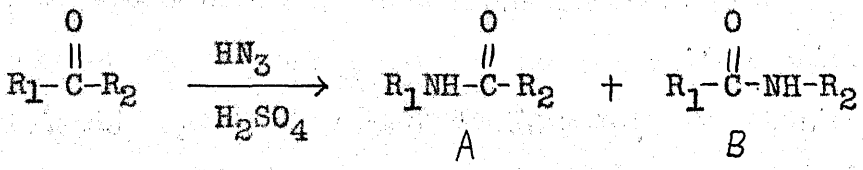


TABLE I

REACTION OF HYDRAZOIC ACID WITH KETONES



	R_1	R_2	Fraction of A in product	Reference
a.	p-chlorophenyl	phenyl	0.59	18
b.	p-nitrophenyl	phenyl	0.51	18
c.	p-methylphenyl	phenyl	0.54	18
d.	p-methoxyphenyl	phenyl	0.61	18
e.	p-diphenylyl	phenyl	0.52	18
f.	p-nitrophenyl	p-methoxyphenyl	0.5	19
g.	p-chlorophenyl	p-methoxyphenyl	0.5	19
h.	o-methylphenyl	phenyl	0.12	19
i.	1-phenanthryl	phenyl	0.17	20
j.	styryl	methyl	0.0	18
k.	1-phenyl-2-propenyl	methyl	1.0	18
l.	methyl	phenyl	0.05	18
m.	ethyl	phenyl	0.15	18
n.	isopropyl	phenyl	0.49	18
o.	t-butyl	phenyl	1.0	18

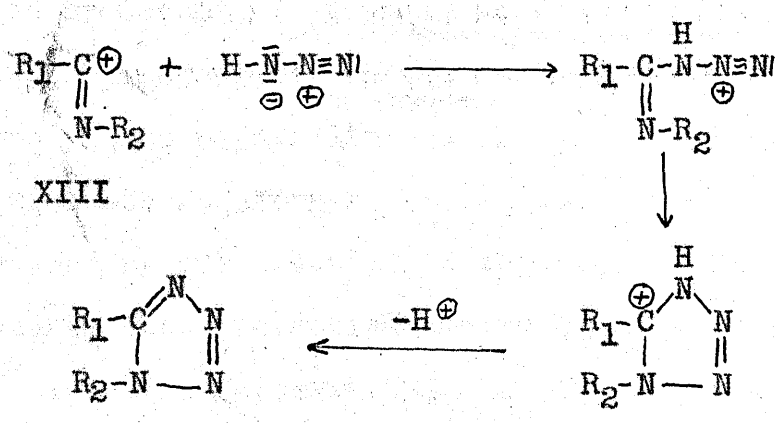
(2)b Similar reaction with XIIb

The speed of these reactions is determined by the basicity of the ketone used and by the migratory aptitude of the group which migrates in step (2). However the products formed do not depend on these factors. In many of the reactions, for example k, l, m, n and o in Table I, steric factors seem to determine the configuration of ion XII and thus the course of the reaction; that is, there seems to be a tendency to favor the formation of an ion XII such that the more bulky R group is trans to the $-N_2$ group. However the electronic character of the group seems to have some effect, for example in the reaction of 1-benzoylphenanthrene (i in Table I).

Tetrazoles are usually formed in a small amount as by-products of the reaction of ketones with an equivalent amount of hydrazoic acid. If they are desired as the main products, the use of two molar equivalents of hydrazoic acid or more will usually give good yields. Acetone gives 1,5-dimethyltetrazole. Cyclohexanone gives 1,5-pentamethylenetetrazole, otherwise known as metrazole. (23) The use of oximes instead of the ketones has been recommended in some cases. (24)

The formation of the tetrazoles can be explained by the reaction of the ion XIII, in the mechanism discussed

above, with a molecule of hydrazoic acid, followed by cyclization and elimination of a proton:



XIII

Only three aldehydes had been reacted with hydrazoic acid previous to the present work. Acetaldehyde gives a 64% yield of acetonitrile and 20% of N-methylformamide in the presence of sulfuric acid. (15) m-Nitrobenzaldehyde gives a mixture of products, 5/6 of which is m-nitrobenzonitrile and 1/6 of which is m-nitroaniline, the total yield being not quite quantitative. (6) When benzaldehyde is reacted using two different concentrations of sulfuric acid, striking results are obtained. When the sulfuric acid to aldehyde molar ratio is 0.72, a 70% yield of benzonitrile and 13% of formanilide is obtained. When the ratio is 5.4, the corresponding yields are 5% and 50%. (15)

Hydrazoic acid acts on some quinones in a manner similar to ketones when the reaction is catalyzed by sulfuric acid.

Thus phenanthrenequinone gives phenanthridone. (25, 27) Chrysenequinone and retenequinone give phenanthridones, claimed by Caronna (26) to be single products, not mixtures of the two possible phenanthridones. Acenaphthenequinone yields naphthalic acid anhydride. (28, 29)

With other quinones, on the other hand, the azide ion reacts by substitution in the ring. When benzoquinone is treated with hydrazoic acid in benzene solution, 2-azidohydroquinone is formed. (30, 31) This is reminiscent of the action of hydrochloric acid on benzoquinone. 1,4-Naphthoquinone treated with hydrazoic acid in glacial acetic acid gives 2-aminonaphthoquinone. 1,2-Naphthoquinone gives 4-amino-1,2-naphthoquinone. 3-Bromo-1,2-naphthoquinone also gives the reaction, but 2-methyl-1,4-naphthoquinone and 4-methyl-1,2-naphthoquinone give no reaction. (32) The mechanism suggested for the formation of these amino compounds was: first the addition of the hydrazoic acid to the naphthoquinone to give an azidohydroquinone, just as in the case of benzoquinone; then an intramolecular oxidation reduction, with the hydroquinone grouping being oxidized and the azide group being reduced, to give the product. The difference in results with benzoquinone and naphthoquinone could be ascribed to the greater reducing power of the naphthohydroquinone. 2-Azidonaphthoquinone could be easily made from 2-chloronaphthoquinone and sodium azide;

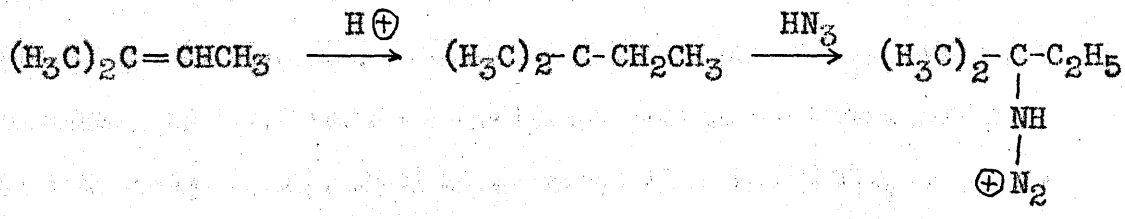
but the azidonaphthohydroquinone could not be isolated by any method. (32)

Caronna (33) reported still another type of reaction of hydrazoic acid with quinones. The action of hydrazoic acid on 2,5-xyloquinone in the presence of concentrated sulfuric acid yielded a compound, $C_8H_9O_2N$, m. p. 216-217°, which is neither a hydroxyquinone nor an aminoquinone. The compound, however, was not identified.

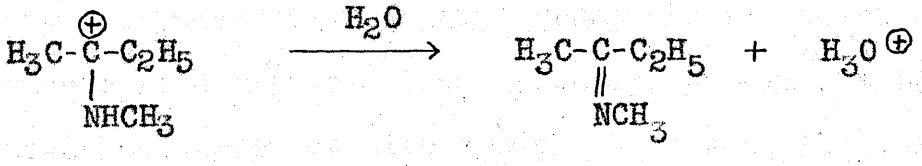
Nitriles react with hydrazoic acid to give either the 5-substituted tetrazoles or the 5-amino-1-substituted tetrazoles depending on whether or not an acid catalyst is present. Dry hydrogen cyanide rapidly forms tetrazole with hydrazoic acid without a catalyst. (34) Mihina and Herbst (35) treated a long series of aliphatic and aromatic nitriles with hydrazoic acid without a catalyst, and got good yields of the 5-substituted tetrazoles. Dicyandiamide reacts with an aqueous solution of hydrazoic acid to give 5-aminotetrazole. (36, 37) Cyanogen under the same conditions gives 5-cyanotetrazole. (38) If a benzene solution of a nitrile is treated with hydrazoic acid in the presence of sulfuric acid, however, a 5-amino-1-substituted tetrazole is obtained. (39)

Acetylenic compounds react with hydrazoic acid without a catalyst much like nitriles. Acetylene itself gives osotriazole. (34) Acetylene dicarboxylic acid reacts more readily, giving osotriazole-4,5-dicarboxylic acid. Propiolic acid and phenylpropiolic acid react similarly. (40)

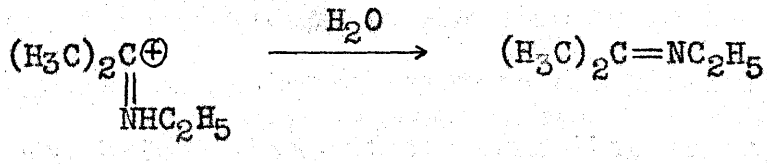
In the presence of sulfuric acid, olefins also react readily with hydrazoic acid to yield Schiff bases. 2-Methylbutene-2 yields a mixture of two Schiff bases which on hydrolysis give acetone, methyl ethyl ketone, ethylamine and methylamine. The probable mechanism of this reaction is the following: (42)



At this point any one of three groups may migrate with expulsion of a nitrogen molecule, either of the two methyl groups or the ethyl group. If one of the methyl groups migrates, the product is the Schiff base of methylamine and ethyl methyl ketone:



If the ethyl group migrates, the product is the Schiff base of ethylamine and acetone:



It will be noted that this reaction differs fundamentally

from the reaction with ketones, because there is no possibility of the splitting out of water and the formation of a double bond between the carbon and nitrogen, thus producing a structure where it is possible for only one group to migrate.

The "intrinsic" migratory aptitudes of various aryl groups have been determined in the case of the pinacol-pinacolone rearrangement of symmetrical pinacols. The values assigned to several of these groups (where phenyl is arbitrarily assigned the value of 1) are: (57)

p-methoxyphenyl	400
p-methylphenyl	15.7
p-diphenylyl	11.5
phenyl	1.0
p-chlorophenyl	0.7

McEwen, Gilliland and Sparr (42) have studied the migratory aptitudes of these aryl groups in the reaction of hydrazoic acid with olefins. Although the yields in these reactions were not high enough to warrant the assignment of definite relative values of migratory aptitudes, nevertheless it was found that the order of the migratory aptitudes of these groups is the same as in the pinacol-pinacolone rearrangement of symmetrical pinacols.

It is obvious that any compound that is capable of giving a carbonium ion in the presence of an acid should react with hydrazoic acid. Thus diphenylcarbinol gives benzalaniline,

menthol gives a mixture of Schiff bases, and anethole dibromide gives the Schiff base of anisidine and alpha-bromopropionaldehyde. (41)

Other compounds with reactive double bonds react with hydrazoic acid without a catalyst. Methyl isocyanide yields 1-methyltetrazole. (43) Dimethyl azodicarboxylate gives a strange reaction in which 5-methoxytetrazole and methyl carbomethoxy carbamate are formed in addition to carbon dioxide and nitrogen. (44)

Compounds with adjacent double bonds are expecially reactive with hydrazoic acid, no catalyst being necessary. Isocyanates yield carbamyl azides, methyl isocyanate yielding N-methyl-carbamyl azide. (45) Ketene reacts with hydrazoic acid to form the acid azide. This on heating rearranges to form methyl isocyanate which can then react with another molecule of hydrazoic acid to form methyl carbamyl azide. (46) N,N'-diphenyl carbodiimide, $C(:NC_6H_5)_2$, prepared by the action of mercuric oxide on N,N'-diphenyl thiourea, reacts with hydrazoic acid to form 1-phenyl-5-anilinotetrazole. (47) Fulminic acid, HONC, reacts to form 5-hydroxytetrazole. (48)

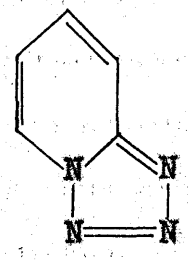
In some cases the azide ion is capable of displacing other bases to give products which are similar to the products obtained in the acid catalyzed reaction. In the Curtius reaction, (49) an acyl azide, which can be prepared

by the action of sodium azide on an acyl halide, is decomposed to give the amine. The decomposition is acid catalyzed, (11) and probably proceeds by the same mechanism as the reaction of hydrazoic acid with carboxylic acids, at least with those acids in whose reaction the oxocarbonium ion serves as the intermediate.

If an ether solution of diphenyl dichloromethane is treated with silver azide, a crystalline diphenyl methyl diazide, m. p. 42°, can be isolated. When this compound is treated with sulfuric acid, hydrazoic acid and nitrogen are evolved and benzanilide is isolated in quantitative yield. (50) The reaction probably proceeds by a mechanism similar to that encountered in the reaction of benzophenone with hydrazoic acid. The intermediate which would be obtained by addition of a proton to one of the azide groups and splitting out a molecule of hydrazoic acid would be the same one as the intermediate XII in the mechanism proposed for the reaction of ketones. When the diazide is heated in amyl ether without an acid, it decomposes at 120° to give 1,5-diphenyltetrazole. (51)

N-Phenylbenzimido chloride reacts with sodium azide in amyl ether at room temperature to give 1,5-diphenyltetrazole also. (52) This procedure works only when the N-substituent is aromatic. If the substituent is aliphatic, the imide chloride is decomposed by the high temperature

necessary for the reaction. Even in the case of some aromatic substituents, such as nitro-substituted phenyl groups, the halide is so unreactive that the displacement is unsuccessful. If however, hydrazoic acid in chloroform solution is used as the reagent instead of sodium azide, the reaction can be carried out at room temperature, and both these difficulties can be overcome. This method of operation permits reaction even with compounds which are not usually considered imide chlorides, such as 2-chloropyridine and 2-chloroquinoline, the products of reaction with these two being, respectively: (56)



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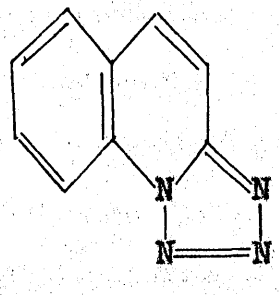
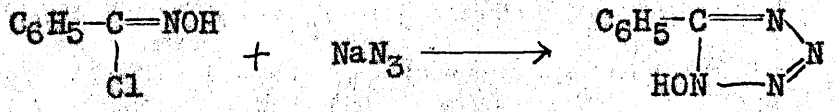
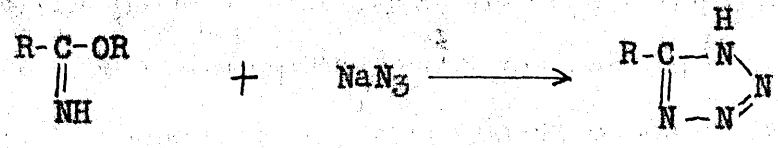


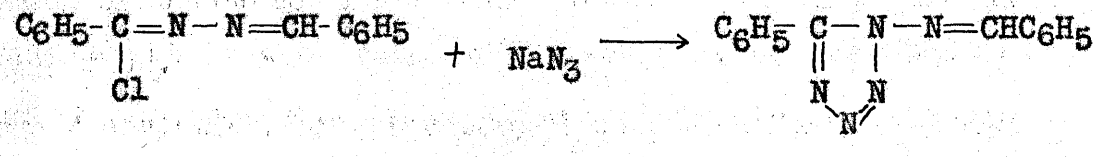
Phenyl hydroxamic chloride reacts with sodium azide to give 1-hydroxy-5-phenyltetrazole. (53)



The reaction with imido esters gives 5-substituted tetrazoles. (54)



The imido chloride resulting from the action of phosphorus pentachloride on N-benzal-N'-benzoyl hydrazine reacts with sodium azide to form 5-phenyl-1-benzalaminotetrazole. (55)



B. THE S_N2 REACTIONS OF UNSYMMETRICAL EPOXIDES

It was once accepted that S_N2 attack on unsymmetrical epoxides took place at the less substituted carbon. This generalization does hold true in the case of all the aliphatic epoxides which have been tested. Thus propylene oxide, when treated with sodium methoxide (58, 59), gives exclusively 1-methoxypropanol-2; and its base catalyzed reactions with malonic ester (60), ethyl cyanoacetate (61), and acetoacetic ester (62) give lactones resulting from attack at the primary carbon and cyclization by elimination of an ethoxide ion. Propylene oxide and other similar aliphatic epoxides react with ethylene diamine (63) to give 1-amino-2-hydroxy compounds, and with hydrazine (64) to give the corresponding 1-hydrazino compounds.

Epichlorohydrin reacts in a similar manner. With sodiomalonic ester (65) it gives 2-carbethoxy-4-hydroxy-5-chloro-gamma-pentanolactone. With sodium phenoxide in alcohol solution it gives 1,3-diphenoxypropanol-2. (66) With ethyl magnesium bromide, it gives decomposition products and tars; but with diethyl magnesium, it gives 1-chloropentanol-2. (67)

In the reactions of styrene oxide types, although in many cases the accepted rule gave consistent results, some inconsistencies were observed. Styrene oxide is attacked by the anions of malonic ester (68), acetoacetic ester (62), and by dimethylamine (69) at the primary carbon atom. Re-

duction with lithium aluminum hydride, which proceeds by S_N2 attack of the aluminum hydride anion, or a derivative of it, gives very largely, if not entirely, the secondary alcohol. (70) 4-Bromo-1-naphthylethylene oxide is converted by dibutylamine and by dialkylamines with longer chains into the secondary alcohol. (71)

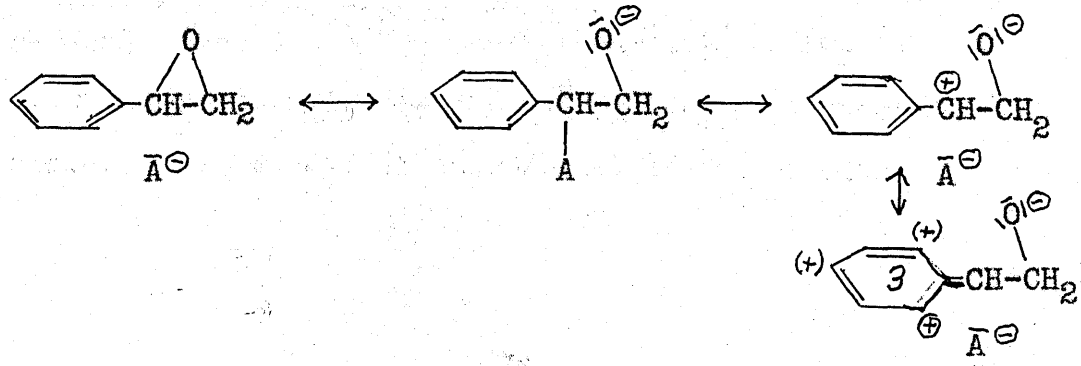
However it is found that as the size of the attacking group decreases, styrene oxide is attacked in part, at least, at the secondary carbon. 3,4-Dimethoxystyrene oxide reacts with methylamine to give a mixture of the two possible aminoalcohols. (72) Sodium methoxide with styrene oxide gives a mixture of the two possible hydroxyethers in which the secondary ether accounts for 25-34% of the total. (73) Phenoxide (74) and beta-naphthoxide (75) ions give still a higher ratio of the secondary ether. There are some anions which have been reported to attack exclusively at the secondary carbon atom. Swern, Billen and Knight (76) made this claim for alloxide ion. Their proof of the structure of the product, however, was not conclusive. The method they used was opened to considerable question when Hayes and Gutberlet (77) disproved their claim that acid catalyzed reaction of allyl alcohol and styrene oxide gives the secondary alcohol.

Grignard reagents, when reacted under conditions which avoid rearrangement of styrene oxide, seem to attack at the secondary carbon. The product of the reaction of methyl magnesium iodide with styrene oxide is 1-phenylpropanol-2. This apparently results from an acid catalyzed rearrangement

of the styrene oxide to phenylacetaldehyde and the addition of the Grignard reagent to the aldehyde. If, however, dimethyl magnesium is used, there is no rearrangement, and 2-phenylpropanol-1 is obtained. (78) With phenyl magnesium bromide, the product obtained is dependent on the order of addition of the reactants. When styrene oxide is added to the phenyl magnesium bromide solution, the product is 2,2-diphenylethanol. Addition in the reverse order gives 1,2-diphenylethanol. (79)

These reactions may not be considered in the same class with the anionic reactions previously discussed because of the ability of the magnesium atom in the Grignard reagent to act as an acid in coordinating with the oxygen atom of the epoxide ring. The complex thus formed may then react by an S_N1 rather than by an S_N2 mechanism.

However consideration of the structure of the transition state in the S_N2 reactions of styrene oxide shows that there are factors which should favor the attack of an anion at the secondary carbon atom. Where A is the attacking anion, the transition state for attack at the secondary carbon atom can receive contributions from the following resonance structures:



The transition state for attack at the primary carbon atom is not capable of allylic resonance such as that represented by the last three structures. On the basis of these considerations, therefore, attack at the secondary carbon atom is favored. Indene oxide, the two carbons of whose epoxide ring are both secondary, when reacted with sodium sulfite, gives sodium 2-hydroxyindane-1-sulfonate. (80) Thus, where the two carbons are essentially equivalent except for the possibility of allylic resonance with one of them, the latter effect shows itself strongly.

Another factor which must be considered in explaining the direction of opening of unsymmetrical epoxides is the steric factor. Brown and Eldred (81) have shown that steric factors are of great importance in determining the speed of S_N2 reactions. Thus in the reactions of styrene oxide discussed above, it is apparent that as the attacking group becomes smaller, the ratio of secondary to primary attack increases.

Further evidence that steric factors influence the direction of opening of unsymmetrical epoxides was presented in the work of Adams and Vander Werf. (62) They showed that, whereas the base catalyzed reaction of acetoacetic ester with styrene oxide proceeded by attack exclusively at the primary carbon, the corresponding reaction with butadiene monoxide gave a mixture of products resulting

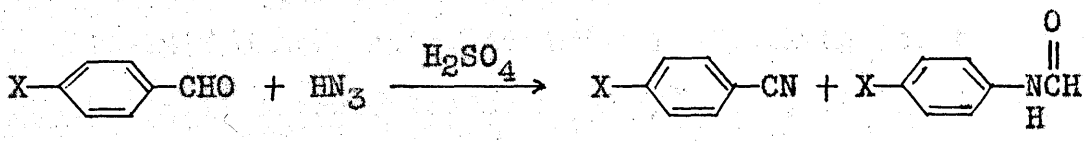
from an equal percentage of attack at the two reactive carbon atoms. Since the electronic effect favoring attack at the secondary carbon is certainly no stronger in the latter case than in the case of styrene oxide, the greater proportion of attack at the secondary carbon atom seems to be due to the lower steric requirements of the vinyl group compared to the phenyl group. The reaction of sodium methoxide and butadiene monoxide also gives a mixture of the two possible ethers. (82, 83) Swern, Billen and Knight (76) reported exclusive attack at the secondary carbon atom by the alloxide ion, their proof of structure again being by an indirect method of doubtful reliability.

Even in the case of butadiene monoxide, however, if the attacking anion is relatively bulky, attack at the primary carbon atom predominates. Thus sodiomalonic ester (68) and sodium n-dodecyl mercaptide (84) give exclusive attack at the primary carbon.

PART II

EXPERIMENTAL

A. THE REACTION OF ALDEHYDES WITH HYDRAZOIC ACID



1. The Reaction of Benzaldehyde with Hydrazoic Acid

(a) At low sulfuric acid concentration. To a stirred mixture of 450 ml. of benzene and 46.7 g. (0.72 mole) of sodium azide, 31.9 ml. (0.58 mole) of concentrated sulfuric acid was added dropwise while the temperature was maintained at 10-15°. Then 30.3 ml. (0.3 mole) of benzaldehyde was added dropwise at the same temperature. Stirring was continued at room temperature until the evolution of gas had ceased (several hours). At this point, addition of a few chips of ice caused further evolution of gas. When this stopped, excess ice was added, the two layers were separated, the aqueous layer was extracted with ether and the ether extracts were added to the benzene layer. The aqueous layer, made alkaline and extracted with ether, yielded no aniline. The combined benzene layer and ether extracts were extracted with 10% sodium hydroxide solution and then stirred for an hour with excess 40% sodium bisulfite solution. Alkaline hydrolysis of the precipitated bisulfite addition product led to the recovery of 8.9 g. (28%) of benzaldehyde. Distillation of the organic layer gave 8.0 g. (26% based on

the total amount of benzaldehyde used) of benzonitrile, b. p. 55-61°/4 mm.; and 4.1 g. (11.3%) of formanilide, b. p. 129-142°/3 mm., m. p. 45-49°. The boiling point of benzonitrile is reported to be 69°/10 mm., 191°/760 mm. (85) The melting point of formanilide is reported (86) as 47°. Based on unrecovered benzaldehyde, the yields of benzonitrile and formanilide were 32% and 14% respectively.

(b) At high sulfuric acid concentration. The procedure was the same as that above, except that 110 ml. (2.0 moles) of concentrated sulfuric acid was used. Treatment of the aqueous layer gave 4.2 g. (15%) of aniline; benzanilide prepared from this gave a melting point of 159-161°. Freundler (87) reported 163°. No benzaldehyde could be recovered from the organic layer; distillation yielded 3.1 g. (10%) of benzonitrile, b. p. 58-65°/5 mm., and 16.0 g. (44%) of formanilide, b. p. 138-148°/5 mm., m. p. 45-50°. The total yield of nitrile was 10%; that of formanlide and aniline was 59%.

2. The Reaction of p-Methoxybenzaldehyde with Hydrazoic Acid

(a) At low sulfuric acid concentration. The procedure was the same as that for benzaldehyde, except that the reaction mixture was stirred for 12 hours at room temperature. Upon addition of ice, a large amount of light yellow

precipitate was obtained. This consisted very largely of sodium sulfate. When an attempt was made to recrystallize the alcohol soluble portion, the only solid product which could be obtained was a yellow solid charring at 240-250°. This solid could be dissolved in water to give a solution which gave a precipitate with barium hydroxide solution. It was concluded to be a sulfonic acid. An aliquot of the precipitate was refluxed with 8 N hydrochloric acid for one hour, and an 8% yield of anisic acid, m. p. 178-180°, was obtained. The melting point of anisic acid reported by Flaschner and Rankin (88) is 184°. Longer refluxing did not significantly increase the yield of anisic acid.

Distillation of the organic layer gave 31.6 g. (78%) of anisonitrile, b. p. 116-122°/5 mm., m. p. 57-61°. The melting point reported (89) is 61°. The anisonitrile thus obtained was hydrolyzed by refluxing with 9 N sulfuric acid for three hours. Anisic acid, m. p. 181-184°, was obtained. The anisic acid obtained by this hydrolysis was converted to phenacyl anisate, m. p. 133-134°. Chen (90) reported 134° as the melting point of phenacyl anisate.

The total yield of nitrile and acid was 86%. No p-methoxyformanilide or derivatives could be isolated.

(b) <u>At high sulfuric acid concentration</u>. This reaction was complete in three hours; during the last hour, the reaction was kept at 45°. Upon addition of ice, 33.0 g. of

precipitate was obtained, which, upon recrystallization from aqueous alcohol, afforded 11.0 g. (24%) of pure anisamide, m. p. 164-165°. The melting point of anisamide reported by Gattermann (91) is 162-163°.

Analysis:* Calculated for $C_8H_9O_2N$: C, 63.5; H, 5.90

Found : C, 63.92, 63.54

H, 5.95, 5.66

On hydrolysis of this anisamide with either sodium hydroxide or hydrochloric acid, anisic acid, m. p. 183-185°, was obtained.

The filtrates from the recrystallization of the anisamide were refluxed for two hours with 10% sodium hydroxide solution. Filtration and acidification of the alkaline solution gave a precipitate, which after recrystallization from alcohol afforded 6.8 g. (15%) of anisic acid, m. p. 182-185°. The 33.0 g. of precipitate contained also about 0.7 g. of an amine, m. p. 153-154°, which was not identified. It was insoluble in water, but soluble in hydrochloric acid or alcohol. Its analysis (C, 67.80, 67.66; H, 5.58, 5.45; N, 10.27, 10.24) did not correspond to the molecular formula of any compound with a reasonably low molecular weight. The needle shaped crystals obtained on recrystallization

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* All analyses were done by the Oakwold Laboratories, Alexandria, Virginia, except when otherwise noted.

were brown; possibly this color was due to an impurity occluded on the surface of the crystals which did not affect the melting point, but which threw the analysis off.

Distillation of the organic layer gave 9.8 g. (25%) of anisonitrile, b. p. 95-103°/1.5 mm., m. p. 57-62°. The total yield of nitrile and derivatives was 64%.

Attempts to recover anisidine from the aqueous solution failed. When the aqueous solution was evaporated to dryness, the residue contained organic material in addition to inorganic salt. This organic material could not be recrystallized. It gave no sharp melting point, only a charring range. Attempts at desulfonation by refluxing with hydrochloric acid failed. No water insoluble products could be obtained.

Two other runs of this same reaction were carried out, which differed only in the highest temperature to which the reaction mixture was raised. The yield of anisonitrile in each case was also far different. In one run, the flask was heated on the steam bath to complete the reaction, and the reaction got out of control, the temperature going up to 75°. There was obtained only 2.6 g. (6.6%) of anisonitrile and a large amount of organic precipitate, probably anisamide, which was not worked up. In another run, the reaction was not heated on the steam bath, and a 56% yield of anisonitrile was obtained. Apparently the anisamide is formed by the hydrolysis of the anisonitrile, which is favored by higher reaction temperatures. Additional support

for this supposition is derived from the known ease of acid catalyzed hydrolysis of anisonitrile.

3. The Reaction of p-Methylbenzaldehyde with Hydrazoic Acid

(a) At low sulfuric acid concentration. One third of the usual molar quantities of reactants was used. The reaction went sufficiently nearly to completion at room temperature, so that no heating was required. The organic layer yielded 0.75 g. (6.2%) of unreacted p-methylbenzaldehyde, and 5.0 g. (44%) of p-methylbenzonitrile, b. p. 68-75°/2 mm. The boiling point reported by Perkin (92) is 218°/760 mm. This was hydrolyzed to p-toluic acid, m. p. 178-180°. The melting point of p-toluic acid reported by Fischli (93) is 180°.

The higher boiling material from the organic layer and the residue from the distillation were hydrolyzed by refluxing with 6 N hydrochloric acid for four hours. The amine fraction thus obtained was benzoylated and 1.1 g. (5.3%) of N-benzoyl-p-toluidine, m. p. 155-157°, was isolated. The melting point of this compound reported by Wallach (94) is 158°. The neutral fraction remaining after the acid hydrolysis of the higher boiling fraction was further hydrolyzed with 10% sodium hydroxide solution and 0.35 g. (2.6%) of p-toluic acid, m. p. 178-180°, was obtained.

Based on original p-methylbenzaldehyde, the yield of nitrile and acid was 47%, that of the formanilide derivative 5.3%. Based on the aldehyde used up, the corresponding yields were 50% and 5.6%, respectively.

(b) At high sulfuric acid concentration. One third the usual molar quantities of reactants was used. The aqueous layer yielded some amine which was benzoylated and yielded 0.35 g. (1.7%) of N-benzoyl-p-toluidine, m. p. 156-158°. No p-methylbenzaldehyde could be recovered. The organic layer yielded 1.3 g. (11%) of p-methylbenzonitrile, b. p. 75-85°/3 mm., and 5.6 g. (41.4%) of p-methylformanilide, b. p. 122-124°/0.1 mm., m. p. 48-50°. The melting point of p-methylformanilide reported by Tobias (95) is 52°. A small amount of intermediate distillate gave 0.28 g. (2%) of p-toluic acid, m. p. 178-180°, on alkaline hydrolysis. The total yield of nitrile and acid was 13%, that of the formanilide and derivative, 43%.

4. The Reaction of p-Chlorobenzaldehyde with Hydrazoic Acid

(a) At low sulfuric acid concentration. Heating on the steam bath was necessary to bring the reaction to completion. Upon addition of ice, a precipitate of p-chloroanilinium sulfate, m. p. 235-242°, mixed with sodium sulfate, was obtained, from which 3.0 g. (8%) of p-chloroaniline, m. p. 70-72°, was recovered. The melting point of p-chloroaniline reported by Beilstein and Kurbatow (96) is 70-71°.

The organic layer on distillation yielded 12.1 g. of distillate at 74-80°/3 mm. and 4.3 g. at 80-90°/ 3 mm. The first fraction had a melting range of 70-82°. The residue from the distillation on recrystallization gave 4.1 g. of material of m. p. 106-109°. The melting point of p-chlorobenzonitrile (97) is 93-94°, and that of p-chloroformanilide (98) is 102°. The fractions obtained by distillation were not judged to be cleanly separated, so they were hydrolyzed with 10 N hydrochloric acid. A 55% yield of p-chlorobenzoic acid, m. p. 241-243°, and 4% of p-chloroaniline, m. p. 67-70°, was thus obtained. The melting point of p-chlorobenzoic acid reported by Beilstein and Schlun (99) is 236-237°. The p-chloroaniline was converted to the acetyl derivative, m. p. 177-179°. The melting point reported by Beilstein and Kurbatow (100) is 178°. The total yield of p-chlorobenzoic acid was 55%, that of p-chloroaniline, 12%.

(b) At high sulfuric acid concentration. The reaction was brought to completion by final heating for two hours at 40°. The precipitate formed upon addition of ice yielded no amine, but gave 0.8 g. (1.8%) of p-chlorobenzoic acid, m. p. 236-241°, upon acid hydrolysis. Recrystallization of the basic fraction obtained when the aqueous layer was made alkaline gave 6.1 g. (16%) of pure p-chloroaniline, m. p. 67-69°. From the organic layer, 4.3 g. (10.0%) of p-chlorobenzaldehyde was recovered; there were

isolated, after acid hydrolysis, 5.7 g. (13.5%) of p-chlorobenzoic acid, m. p. 238-243°, and 10.5 g. (27%) of p-chloroaniline, m. p. 67-69°. Based on original aldehyde, the yield of p-chlorobenzoic acid isolated was 13.5% and of p-chloroaniline 43%. Based on aldehyde used up in the reaction, the corresponding yields were 15% and 48%, respectively.

5. The Reaction of p-Nitrobenzaldehyde with Hydrazoic Acid

(a) At low sulfuric acid concentration. One half of the usual molar quantities of reactants was used in this experiment. Nitrogen was evolved in good yield at room temperature. The organic layer yielded 4.6 g. (22%) of recovered p-nitrobenzaldehyde. Upon removal of most of the benzene, addition of water, and steam distillation, 12.0 g. (54%) of pure p-nitrobenzonitrile, m. p. 148-149°, was isolated from the distillate. The melting point of p-nitrobenzonitrile reported by Borsche (101) is 149°. When the nitrile was refluxed with 20% sodium hydroxide, unidentifiable products were formed. Hydrolysis with 6 N hydrochloric acid, however, proceeded smoothly, yielding p-nitrobenzoic acid, m. p. 240-241°. The melting point reported by Wilbrand and Beilstein (102) is 240°.

Acid hydrolysis of the crude material remaining in the mother liquor from the recrystallization of the nitrile yielded 0.6 g. (2%) of p-nitrobenzoic acid, m. p. 235-237°.

The aqueous residue remaining from the steam distillation yielded some crystals, which on recrystallization gave 0.3 g. (1.5%) of p-nitroaniline, m. p. 146-149°. The melting point reported by Hubner (103) is 147°. Acetylation formed p-nitroacetanilide, m. p. 212-214°. The melting point reported by Kaufmann (104) is 215-216°.

The total yield of nitrile and acid obtained in this experiment was 56%. That of p-nitroaniline was 1.5%. Based on unrecovered aldehyde, the corresponding yields were 72% and 1.9%, respectively.

(b) At high sulfuric acid concentration. Again only one half of the usual molar quantities of reactants was used. A quantitative yield of gas was obtained as soon as all the aldehyde had been added, even below room temperature. A large amount of precipitate was obtained on addition of ice to the reaction mixture. This was combined with amine fractions obtained from the benzene layer and the aqueous layer. The amine was best purified by dissolution in 6-9 N hydrochloric acid, reprecipitation by making the solution alkaline, and then recrystallization from alcohol and water. A yield of 4.7 g. (23%) of p-nitroaniline, m. p. 144-147°, was obtained in this manner. Steam distillation of the benzene solution yielded 10.3 g. (46%) of p-nitrobenzonitrile, m. p. 146-149°. No p-nitrobenzaldehyde could be recovered.

6. The Effect of Concentrated Sulfuric Acid on Benzamide

A clear colorless solution was formed when 0.5 g. of benzamide (m. p. 127-128°) was dissolved in 2 ml. of concentrated sulfuric acid. After standing overnight at room temperature and warming to 33° for one hour, the solution was cooled and diluted with ice. A white precipitate came down, consisting of 0.22 g. of benzamide. Extraction of the solution with warm benzene gave 0.08 g. of benzamide. Making the solution alkaline with sodium hydroxide and extraction with ethyl acetate gave an additional 0.05 g. of benzamide. Total recovery of benzamide was 0.35 g. (70%). At no time was there a layer of benzonitrile, and the melting point of all the benzamide recovered was, without recrystallization, identical with that of the starting material, indicating that no hydrolysis or dehydration had taken place.

B. THE ACID-CATALYZED REACTION OF STYRENE OXIDE WITH HYDRAZOIC ACID

1. The Reaction of Styrene Oxide with Hydrazoic Acid in the Presence of Concentrated Sulfuric Acid

(a) At high sulfuric acid concentration. A mixture of 14.8 g. (0.228 mole) of sodium azide and 75 ml. of chloroform was cooled in an ice bath, stirred vigorously, and 40 ml. of concentrated sulfuric acid was added. Then 16.2 ml. (0.143 mole) of styrene oxide (b. p. 74-78°/10 mm.) dissolved in 25 ml. of chloroform was added dropwise at a temperature of 20-25°. There was vigorous evolution of heat, and the addition took several hours.

Ice was added, the layers were separated, the aqueous layer was extracted with ether, and the ether added to the chloroform layer. Distillation of the organic layer yielded nothing but a dark tarry residue.

The aqueous layer was made alkaline with concentrated sodium hydroxide solution and steam distilled. No significant quantity of organic product could be obtained from the distillate.

When this procedure was repeated using 60 g. (0.5 mole) of styrene oxide and proportionately larger quantities of the other materials, about 1 gram of aniline was recovered from the aqueous layer. Benzanilide, m. p. 163-164°, was prepared from this product.

(b) At low sulfuric acid concentration. The same procedure was used as in the reaction described immediately above except that 37.4 g. of sodium azide, 200 ml. of chloroform, 70 ml. of concentrated sulfuric acid and 60 g. of styrene oxide were used. The amount of tar formed in the reaction was noticeably less. The aqueous layer was made alkaline and extracted with ether. After removal of the ether, distillation of the residue yielded 3.8 g. (8%) of aniline.

(c) At low temperature. The same procedure was used as that described immediately above except that 19.5 g. of sodium azide, 27.8 ml. of concentrated sulfuric acid, 100 ml. of chloroform, and 30 g. of styrene oxide were used, and the temperature was kept below 10° at all times. Aniline, 0.7 g. (3%), was again the only isolable product.

2. The Reaction of Styrene Oxide with Hydrazoic Acid in the Presence of Anhydrous Stannic Chloride

(a) Decomposing the reaction mixture with water. When a catalyst other than sulfuric acid was used, it was necessary to prepare the hydrazoic acid separately. The procedure used was that described by Wolff. (9) The hydrazoic acid was prepared in solution in either benzene or chloroform, and its concentration in the solution was determined by titration with standard sodium hydroxide solution using phenolphthalein as indicator.

A solution of 0.26 mole of hydrazoic acid and 26 ml. (0.22 mole) of anhydrous stannic chloride in 350 ml. of benzene was stirred at 20° while 25 ml. (0.22 mole) of styrene oxide was added dropwise. The reaction was allowed to proceed at room temperature until the evolution of gas was complete (several hours). Ice was then added in excess. The aqueous layer was made alkaline with 50% sodium hydroxide solution and steam distilled into alcoholic hydrochloric acid. Evaporation of the distillate and recrystallization of the residue from absolute alcohol afforded 4.8 g. (17%) of aniline hydrochloride and 0.22 g. (2%) of ammonium chloride. The organic layer was washed with sodium hydroxide solution and distilled. After the benzene was removed, a few grams of a mixture of nitrogenous products distilled at 75-125°/3 mm. The properties of this mixture are described in the following experiment. The residue from the distillation yielded a trace of trans-2,5-diphenyldioxane, m. p. 174.4-174.6°. The melting point of this compound reported in the literature (105) is 173°.

Analysis: Calculated for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7
Found : C, 80.30, 80.32;
H, 7.10, 7.17

(b) Decomposing the reaction mixture with alcohol. In this run, it was proposed to alcoholize the products of the reaction and thus form acetals from any aldehydes

formed in the reaction. An attempt was made also to isolate the aniline formed in the reaction as addition compounds with stannic chloride, $(C_6H_5NH_2)_4SnCl_4$, and with chlorostannic acid, $(C_6H_5NH_3Cl)_4SnCl_4$.

A solution of 1.06 mole of hydrazoic acid in 785 ml. of benzene was stirred with 0.53 mole of anhydrous stannic chloride, and 63.6 g. (0.53 mole) of styrene oxide added dropwise at a temperature below 10°. Then the reaction was allowed to warm to room temperature and continued overnight. In the morning a dark red syrup had settled, and nitrogen was still evolving. At this point 124 ml. (2.12 moles) of absolute alcohol was added. The red syrup first dissolved, the whole reaction mixture becoming a homogeneous red solution; then a yellow precipitate formed. A rough tin determination (106) showed this precipitate to contain about 40% tin. An aliquot of this precipitate was dissolved in water, the solution made alkaline and steam distilled. A 6% yield of aniline was obtained.

The mother liquor was saturated with dry hydrogen chloride. Two layers formed again, a deep red bottom layer containing a precipitate, and a nearly colorless top layer. The precipitate contained about 24% of tin and some aniline salt. The amount of the latter was not determined exactly, but it would account for a yield of between 5 and 10%.

The lower red layer was poured into excess 10% sodium carbonate solution. A black organic layer separated, which, together with ether extracts of the aqueous layer, was distilled. A few drops distilled at 67-68°/4 mm., which solidified, and had a melting point of 144°. Another small fraction, a white solid, distilled over at 180-184°/4 mm. This had a melting point of 158-159° and contained nitrogen. The amounts of these products were insignificant.

The nearly colorless benzene solution was washed with an excess of sodium hydroxide solution and distilled. The only product obtained was 8.5 g. of nitrogenous material boiling at 105-127°/5 mm. This product solidified on cooling in ice and melted at 20-26°. On careful redistillation it could be separated into several fractions. This complex mixture of products was not further investigated.

The residue from the distillation of the benzene solution afforded some 2,5-diphenyldioxane, as in the previous experiment.

3. The Reaction of Styrene Oxide with Hydrazoic Acid in the Presence of Other Catalysts

When crushed anhydrous zinc chloride was used as the catalyst, a small amount of a solid amine, b. p. 157-164°/11 mm., m. p. 59-64°, was the only product which could be isolated. It was insoluble in water, but soluble in hydro-

chloric acid. A benzoyl derivative could not be prepared. Such a small quantity was obtained that no further work could be done on it.

Thionyl chloride gave some sort of reaction, but no pure product could be isolated.

Trichloracetic acid gave no reaction whatsoever even when the reaction mixture was heated to 45°. No attempt was made, therefore, to work up the reaction mixture.

C. THE PREPARATION OF CYCLOHEXENE OXIDE

1. By the Reaction of Cyclohexene with Oxygen in the Presence of Benzaldehyde

An attempt was made to prepare cyclohexene oxide by the method of Raymond. (107) This method consists essentially in passing air through a mixture of benzaldehyde and cyclohexene. Raymond's conditions were duplicated as far as possible except that the air was passed in through an ordinary glass tubing instead of through a sintered glass disc, as he suggested. On distillation of the reaction mixture, nothing but cyclohexene and benzaldehyde and higher boiling material could be recovered.

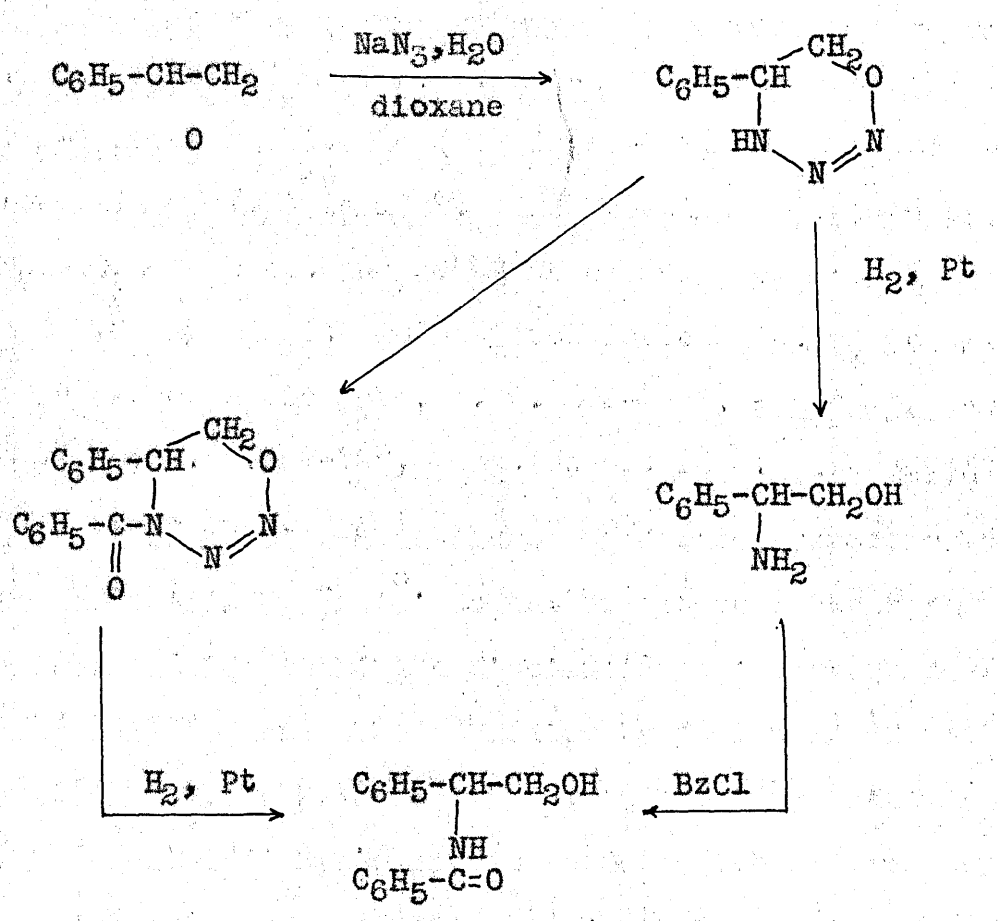
2. By the Dehydrohalogenation of 2-Chlorocyclohexanol.

The 2-chlorocyclohexanol was prepared and dehydrohalogenated by the method of Newman and Vanderwerf. (108) An overall yield of 20% of cyclohexene oxide on the basis of the cyclohexene was obtained on the first run.

D. THE ACID CATALYZED REACTION OF CYCLOHEXENE OXIDE WITH HYDRAZOIC ACID

A mixture of 26 g. (0.4 mole) of sodium azide and 200 ml. of chloroform was stirred while 47.7 ml. of concentrated sulfuric acid was added. Then 32.7 g. (0.19 mole) of cyclohexene oxide was added dropwise at room temperature. Ice was added and the layers separated. If an attempt was made to distil the chloroform layer, either with or without previous washing with sodium bicarbonate solution, a black tar was formed on raising the temperature to 100°. If the chloroform layer was evaporated to dryness in vacuo, a light yellow viscous syrup was obtained. It could not be crystallized, benzoylated, or converted to a phenylhydrazone or an oxime. It was soluble in ether but insoluble in hydrochloric acid or sodium hydroxide solution. No further work was done on this material.

E. THE REACTION OF STYRENE OXIDE WITH SODIUM AZIDE AND PROOF OF STRUCTURE OF THE PRODUCT



1. The Reaction of Styrene Oxide with Sodium Azide

To a refluxing solution of 100 g. (0.83 mole) of styrene oxide in 1300 ml. of dioxane, a solution of 68 g. (1.15 mole) of sodium azide in 175 ml. of water was added dropwise. Refluxing was continued for twenty hours, after

which the two layers were separated. The dioxane layer on distillation gave 95 g. of crude material boiling at 130-139°/5 mm. On careful redistillation of this fraction through a six inch Vigreux column, 90 g. (63%) of 5-phenyl-5,6-dihydro-1,4,2,3-oxatriazine, b. p. 105-107°/1 mm., was obtained.

Analysis: Calculated for $C_8H_9ON_3$: C, 58.9; H, 5.56; N, 25.8

Found : C, 58.41, 58.62; H, 6.21, 6.11; N, 26.21, 26.16

This compound was insoluble in water, hydrochloric acid and sodium hydroxide solution. It could be refluxed for three hours with 3 N hydrochloric acid containing 50% dioxane, or for half an hour with 5% sodium hydroxide in 50% alcohol, and still be recovered unchanged. On warming slightly with concentrated hydrochloric acid or with acetic anhydride containing 20% concentrated sulfuric acid, decomposition occurred with evolution of nitrogen. The oxatriazine could be distilled at 159-160°/21 mm. with very little pyrolysis, 5 ml. giving 4.1 ml. of distillate.

The 3,5-dinitrobenzoyl derivative crystallized from ethyl acetate or an ethyl acetate-ligroin mixture as very light yellow needles, m. p. 137.4-138.2°.

Analysis: Calculated for $C_{15}H_{11}O_6N_5$: C, 50.4; H, 3.11; N, 19.6.

Found : C, 50.31, 50,52; H, 3.07, 3.13;
N, 19.77, 19.86

2. The Preparation of 2-Amino-2-phenylethanol by Reduction of 5-Phenyl-5,6-dihydro-1,4,2,3-oxatriazine

Hydrogenation of 16.3 g. (0.1 mole) of oxatriazine in 50 ml. of ethanol at three atmospheres pressure in the presence of 0.1 g. of platinum oxide proceeded without any drop in pressure. After hydrogenation for 24 hours, the solution was filtered and distilled. The yield of 2-amino-2-phenylethanol, b. p. 115-126°/3 mm., was 11.1 g. (81%). This compound is a difficultly crystallizable oil, which, on standing in air, forms a solid, probably a carbonate, m. p. 104-109°. Adkins and Pavlic (109) reported 101-104°/2 mm. as the boiling point and 108-111° as the melting point of the aminoethanol, but they probably confused the melting point of the latter with that of the carbonate. The diacetate had a melting point of 104-105°. Reihlen, Knopfle and Sapper (110) reported 103°. The picrate had a melting point of 205-206°. Ovakimian, Kuna and Levene (111) reported 208-210°. Gabriel and Colman (112) reported 207°.

Analysis:* Calculated for $C_{14}H_{14}O_8N_4$: C, 45.9; H, 3.85;
N, 15.3

Found: C, 46.20, 46.19; H, 3.77, 3.81; N, 15.4, 15.4.

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* This analysis was done by The Weiler and Strauss Microanalytical Laboratory, Oxford, England

3. 4-Benzoyl-5-phenyl-5,6-dihydro-1,4,2,3-oxatriazine

A solution of 3.17 g. (0.0195 mole) of the oxatriazine in 15 ml. of pyridine was treated with a 10% excess of benzoyl chloride, heated on the steam bath for 30 minutes, then poured into 45 ml. of water. The water layer was extracted with benzene. The liquid obtained by evaporation of the benzene could not be crystallized. It was distilled in one case, and some of the benzoyl derivative distilled over at 160-164°/0.03 mm., in spite of considerable decomposition. However, when distillation of a second run was attempted, the whole product decomposed; and only benzoic acid was obtained in the distillate. Attempts to isolate an analytical sample of the benzoyl derivative were then abandoned.

4. The Preparation of 2-Benzamido-2-phenylethanol by Reduction of 4-Benzoyl-5-phenyl-5,6-dihydro-1,4,2,3-oxatriazine

The liquid benzoyl derivative obtained above was dissolved in 40 ml. of 95% alcohol, 0.03 g. of platinum oxide added, and the mixture hydrogenated for 24 hours. A large amount of white precipitate was present at the end of the hydrogenation. More alcohol was added and the solution warmed to dissolve the product. The solution

was filtered and water added to nine-tenths of the solution. The crystals of 2-benzamido-2-phenylethanol obtained on cooling weighed 2.66 g. (63%), m. p. 152-154°. Reihlen, Knopfle and Sapper (110) reported 153°. The solid obtained on evaporation of the filtrate yielded 0.76 g. (18%) of product, m. p. 150-152°, on recrystallization from benzene plus low boiling petroleum ether. The total yield of pure product thus obtained was 81%, indicating that the benzoyl derivative was quite homogeneous. The product of melting point 152-154° was insoluble in hydrochloric acid.

When the benzoyl derivative obtained by distillation at 160-164°/0.03 mm. was hydrogenated, the crystals obtained directly from the alcohol solution melted at 153.8-154.1°, apparently being a little purer than those obtained by direct hydrogenation of the benzoylation mixture. A mixed melting point of the two batches gave a range of 152-154.5°, establishing the identity of the two.

5. The Preparation of 2-Benzamido-2-phenylethanol by the Benzoylation of 2-Amino-2-phenylethanol

To a mixture of 0.5 g. of 2-amino-2-phenylethanol and 10 ml. of 10% sodium hydroxide, 0.55 ml. of benzoyl chloride was added. The mixture was shaken until the reaction was completed and the flask had cooled to room temperature. The precipitate was filtered and dissolved in ethanol. Enough water was added to crystallize out

about half of the material. This, on two additional recrystallizations from alcohol and water, gave 2-benzamido-2-phenylethylbenzoate, m. p. 153.5-154°. Reihlen, Knopfle and Sapper (125) reported 154°. A mixed melting point of this dibenzoate with the monobenzoate isolated in the previous experiment gave a melting range of 132-142°.

The ethanol-water solution containing the other half of the benzoylation product was evaporated to dryness, and the solid thus obtained was recrystallized from benzene plus petroleum ether. One recrystallization gave the monobenzoate, m. p. 152.5-153°. A mixed melting point with the monobenzoate obtained in the previous experiment gave a melting range of 152.8-154.1. Both the monobenzoate and the dibenzoate were insoluble in hydrochloric acid.

F. THE ATTEMPTED REACTION OF ALDEHYDES WITH SODIUM AZIDE

A solution of 14.1 g. (0.1 mole) of p-chlorobenzaldehyde in 200 ml. of dioxane was refluxed while 7.8 g. (0.12 mole) of sodium azide in 30 ml. of water was added dropwise. The solution was refluxed for 24 hours. The layers were separated, and the aqueous layer was extracted with dioxane. The dioxane was evaporated and the residue treated with 50 ml. of 40% sodium bisulfite solution. The solid formed on this treatment was extracted with benzene. Only 0.5 g. of material dissolved in the benzene, the rest being the sodium bisulfite addition compound of the aldehyde. This 0.5 g. of material was considered negligible, probably consisting mostly of p-chlorobenzoic acid resulting from air oxidation of the aldehyde.

The same experiment was performed on anisaldehyde. Over 80% of the aldehyde was recovered by distillation.

PART III

DISCUSSION OF RESULTS

A. SUMMARY OF EXPERIMENTAL RESULTS

In the acid catalyzed reaction of benzaldehyde with hydrazoic acid reported by Schmidt (15) and described on p. 15 of this thesis, there was a curious inversion in the relative percentages of reaction products with change in sulfuric acid concentration. The purpose of the present study was to investigate the generality among aromatic aldehydes of this type of inversion, to obtain evidence for a mechanism which would explain it, and to study the related acid- and base-catalyzed reactions of epoxides with hydrazoic acid.

Schmidt's experiments on benzaldehyde were repeated and the reactions of four other aromatic aldehydes with hydrazoic acid were studied. The conditions used were not identical with those used by Schmidt in that he used pure solutions of hydrazoic acid in benzene to which he added the aldehyde and the catalytic amount of concentrated sulfuric acid, while in this work the hydrazoic acid was generated *in situ*. As a result of this change, the effective catalyst at what is termed the low concentration of sulfuric acid is sodium bisulfate; whereas at the high concentration of sulfuric acid, the concentration of sulfuric acid in the reaction mixture is lower than that used by Schmidt, and, in addition, sodium bisulfate is present.

At the low concentration of sulfuric acid the molar ratio of aldehyde to sodium azide to sulfuric acid used was 1 to 2.4 to 1.92. In the equilibrium established in the reaction mixture the molar ratio of aldehyde, sodium bisulfate, sodium sulfate should be 1 to 1.44 to 0.48. At the high concentration of sulfuric acid the ratio of aldehyde to sodium azide to sulfuric acid was 1 to 2.4 to 6.67. In the reaction mixture the ratio of aldehyde to sodium bisulfate to sulfuric acid should be 1 to 2.4 to 4.27. In the case of benzaldehyde, this difference in conditions gave results which were quantitatively somewhat different from those obtained by Schmidt. However, qualitatively the results were similar. The yields of products obtained at the low sulfuric acid concentration might have been increased by a period of heating at the end of the reaction. It is worthy of note, therefore, that sodium bisulfate seems to give results very similar to those obtained by a small amount of sulfuric acid.

The results of the experiments with the five aldehydes studied are summarized in Table II. The results with benzaldehyde, p-methylbenzaldehyde, and p-chlorobenzaldehyde paralleled those of Schmidt on benzaldehyde. With p-nitrobenzaldehyde, increasing the concentration of sulfuric acid increased the ratio of formanilide to nitrile,

TABLE II

Reaction of Aldehydes with Hydrazoic Acid

Aldehyde	Ratio of Sulfuric Acid to Aldehyde	Yield, %[a]	
		Nitrile	Formanilide
Benzaldehyde	0.72	36	16
	5.4	10	59
p-Methoxybenzaldehyde	0.72	86	0
	5.4	64	0
p-Methylbenzaldehyde	0.72	50	6
	5.4	13	43
p-Chlorobenzaldehyde	0.72	55	12
	5.4	15	48
p-Nitrobenzaldehyde	0.72	72	2
	5.4	46	23

(a) Yields are based on unrecovered aldehyde and include yields of hydrolysis products as well as of unhydrolyzed nitrile and amide. In every case, the amount of nitrogen evolved during the course of the reaction was equal to or greater than that indicated stoichiometrically for the yield of products reported.

but did not invert the ratio. With p-methoxybenzaldehyde the nitrile was the sole product at both sulfuric acid concentrations. It is possible that the p-methoxyformanilide produced in this reaction could not be isolated because it was so easily sulfonated, and the sulfonated products were not amenable to the usual procedures for dealing with the formanilide. At any rate there could not possibly have been an inversion in ratio of products because the yield of anisonitrile and derivatives was already 64%.

Since the reactions of epoxides are in many respects similar to those of aldehydes, the reaction of hydrazoic acid with styrene oxide and cyclohexene oxide was studied in the hope that additional light might be shed on the mechanism of the reactions of hydrazoic acid.

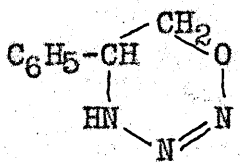
The sulfuric acid catalyzed reaction of cyclohexene oxide with hydrazoic acid gave an unstable viscous product which could not be identified.

When styrene oxide was reacted with hydrazoic acid in the presence of the high concentration of sulfuric acid usually employed in the Schmidt reaction, only tarry materials formed. There were also no isolabe products when thionyl chloride, zinc chloride or trichloroacetic acid were used as catalysts. When a low concentration of sulfuric acid was used, a low yield of aniline was isolated as the only product. When the reaction was carried out at the same low concentration

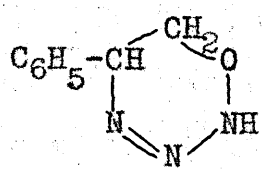
of sulfuric acid and at a low temperature in order to take advantage of a possible favorable difference in the temperature coefficient of the desired reaction and the polymerisation reaction, the yield was not quite as high as when the reaction was carried out at room temperature.

When anhydrous stannic chloride was used as the catalyst, however, the yield of aniline was raised to 17%; and there was obtained a low yield of a mixture of neutral nitrogen containing compounds which were not separated or identified. It was thought that some of the loss in yield in all these styrene oxide reactions might have been due to side reactions involving the aldehydes or ketones which were formed on the hydrolysis of the Schiff bases. If this were true, then decomposition of the Schiff bases with absolute alcohol instead of with water should produce acetals and ketals, which would not be expected to be as liable to give the undesirable side reactions. Therefore an experiment was carried out using stannic chloride as the catalyst, and treating the reaction mixture with absolute alcohol at the point where water was used in the previous experiments. This procedure, however, resulted in no improvement in the yields.

The reaction in aqueous dioxane of styrene oxide with sodium azide, however, gave an excellent yield of a nitrogenous product XIV, insoluble in dilute alkali and acids, but decomposed by warm concentrated mineral acids. It analyzed for $C_8H_9ON_3$. On hydrogenation of the material at three atmospheres pressure in the presence of a platinum catalyst, nitrogen was evolved and beta-phenyl-beta-aminoethanol was produced. It gave a crystalline 3,5-dinitrobenzoyl derivative, and a liquid benzoyl derivative. On hydrogenation of the benzoyl derivative, 2-phenyl-2-benzamidoethanol was produced in good yield and in a state of high purity. On the basis of these results, the product of the reaction of styrene oxide and sodium azide can be assigned either the structure XIV or XV:



XIV



XV

or can be considered a tautomeric mixture of the two. An azide structure is excluded by the formation of the N-benzoyl rather than the O-benzoyl derivative ofbeta-amino-beta-phenylethanol on hydrogenation of the benzoyl derivative of XIV. The compound XIV can be refluxed with dilute acids without change. This behavior also

provides an argument against the azide structure. The infra red absorption bands which are ascribed to the azide grouping (11,8) in methyl azide occur at 4.67, 7.72, and 15.29 microns. The only bands in the infra red spectrum of XIV (Figure I) which are near these are at 4.8, 7.4, 7.6 and 8.0 microns. XIV shows no bands above 14.5 microns. The oxatriazine ring might very well have an infra red spectrum with this limited similarity to that of organic azides. In any event, the chemical proof of the structure of XIV seems unimpeachable, and is to be preferred to conclusions drawn from comparison of spectra.

The structure XV for the oxatriazine is not excluded by the formation of the 4-benzoyl rather than the 2-benzoyl derivative. However the structure XIV seems the more likely one because the double bond in the 2,3-position would be stabilized by resonance involving both the oxygen atom and the adjacent nitrogen atom, whereas the double bond in the 3,4-position would be stabilized by resonance involving only the adjacent nitrogen atom. This does not exclude the presence of a considerable amount of XV in a tautomeric equilibrium, but for purposes of simplicity of nomenclature, it seems that the compound should be called 5-phenyl-5,6-dihydro-1,4,2,3-oxatriazine.

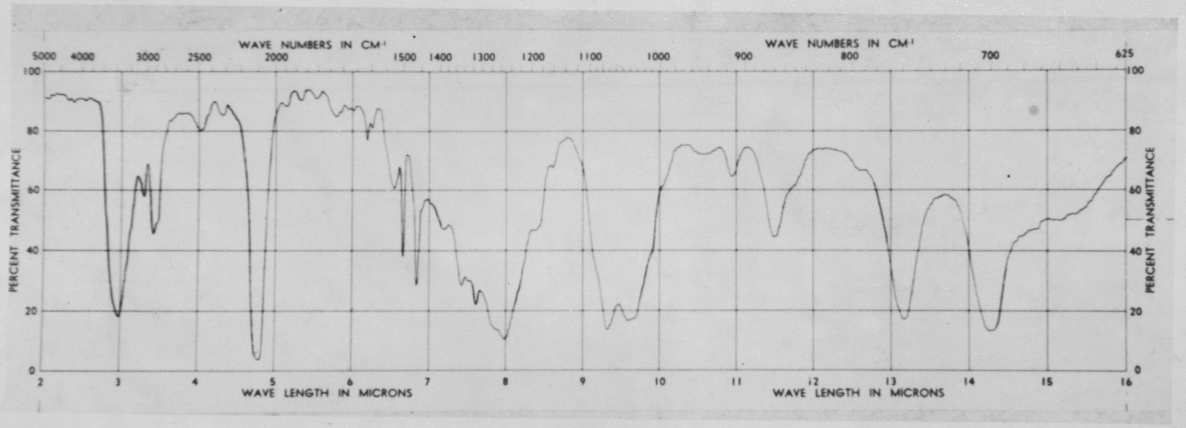


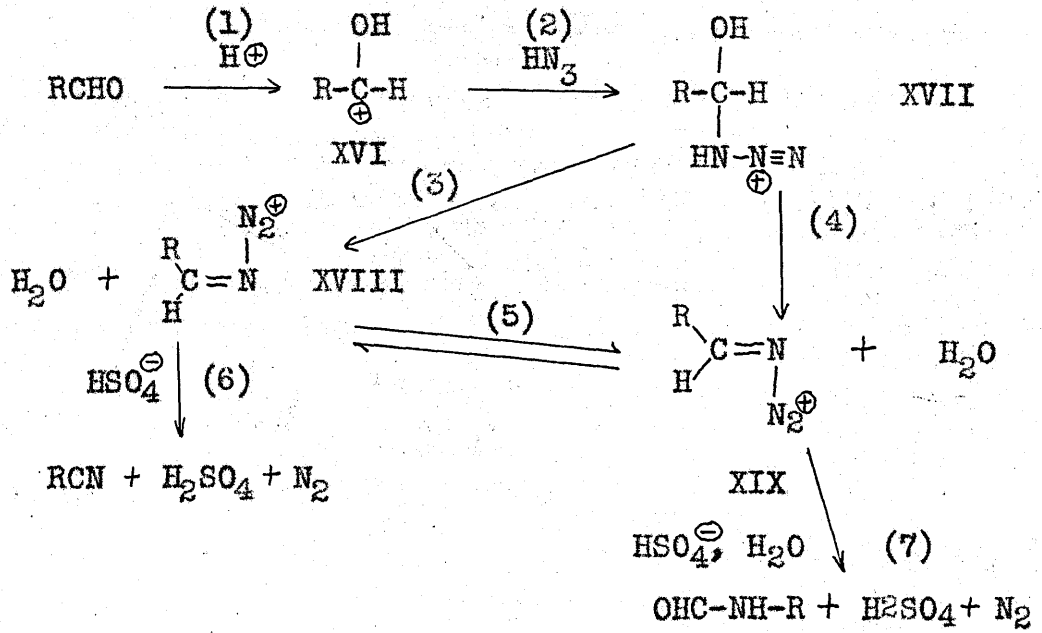
FIGURE I

The Infra Red Spectrum of 5-Phenyl-5,6-dihydro-1,4,2,3-oxatriazine. Done by Samuel P. Sadtler and Sons, Inc., Philadelphia, Pa.

B. THE MECHANISM OF THE REACTION OF ALDEHYDES WITH HYDRAZOIC ACID

A mechanism for the reaction of aldehydes with hydrazoic acid should explain not only the products obtained but why the increase in concentration of sulfuric acid causes a general increase in the ratio of formamide to nitrile formation, and why the inversion in ratio of products fails to occur with both strong electron donating and electron withdrawing groups in the para position.

The mechanism presented here incorporates the features of the mechanism proposed by Smith and coworkers (18, 19, 20, 21) for the ketone reaction and described above on p. 12; and also adds a few proposals which are intended to explain the changes in ratio of products with change in the concentration of catalyst. The outline of the proposed mechanism is the following:



The aldehyde reacts with sulfuric acid to form the conjugate acid XVI. This then combines with hydrazoic acid to give the complex XVII, which then undergoes dehydration to the syn and anti isomers, XVIII and XIX. The species XVIII affords the nitrile by the trans elimination of a proton and a molecule of nitrogen, while the species XIX yields the formanilide by a trans migration of the aryl group, accompanied or followed by the addition of a molecule of water.

To explain the change in ratio of products with change in the concentration of sulfuric acid, the following assumptions must be made:

(1) The free energy of XIX is lower than that of XVIII. This seems reasonable on the basis of the results of Smith and Horwitz (18) on the reactions of alkyl aryl ketones with hydrazoic acid, in which the observed migration ratios underwent a progressive change from preferred phenyl migration to preferred alkyl migration with increasing branching on the alpha position of the alkyl groups.

(2) The rate of formation of XVIII is greater than that of XIX.

(3) Interconversion of XVIII and XIX can occur subject to acid catalysis. Such a conversion would be very similar to that demonstrated by Hauser and Vermillion

(113) to occur between benzoyl-syn- and benzoyl-anti-benzaldoximes.

(4) When the reactions are catalyzed by a small amount of sulfuric acid or sodium bisulfate, the rate of nitrile formation from XVIII exceeds the rate of interconversion of XVIII to XIX. Hence the major product is the nitrile.

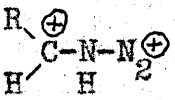
(5) As the concentration of sulfuric acid is raised, the rate of interconversion of XVIII to XIX also rises. If it rises so much as to exceed the rate of conversion of XVIII to the nitrile, then the major part of XVIII will be converted to the more stable XIX, and the yield of the formanilide may exceed the yield of nitrile.

The anomalous behavior of anisaldehyde and p-nitrobenzaldehyde can be explained in one of two ways. One explanation is that, for some reason, the relative stability of XVIII with respect to XIX is increased when R is p-methoxyphenyl or p-nitrophenyl; but this does not seem reasonable as an explanation for both anomalous cases, because the methoxyl and nitro groups exert markedly different electrical effects, thus rendering it improbable that both would tend to stabilize XVIII relative to XIX.

A second possible explanation is that, in the two anomalous cases, the speed of reaction (6) is much greater than the speed of reaction (5), so that even though (5)

is speeded up by the high concentration of acid, the effect is not great enough to overcome the original difference in the two velocities. It is reasonable to assume that the speed of reaction (6) should be unusually fast in the case of the p-methoxyphenyl group, since this group is strongly electron-donating, and the elimination reaction forming the nitrile represents a net transfer of electron density away from the p-methoxyphenyl group.

For the case of the p-nitrophenyl group the explanation can be suggested that the speed of step (5) is so slow that increase of acid concentration is not capable of increasing its speed enough to compete with the speed of (6). The interconversion of XVIII and XIX would probably proceed via the conjugate acid XVIIIa:

XVIIIa 

This interconversion would be accelerated by electron donating substituents and retarded by electron withdrawing substituents in the para position. Therefore both steps (5) and (6) are accelerated by the paramethoxyl group; and they are both slowed by the paranitro group. It would be impossible to predict where a balance in these opposing effects would lie. The

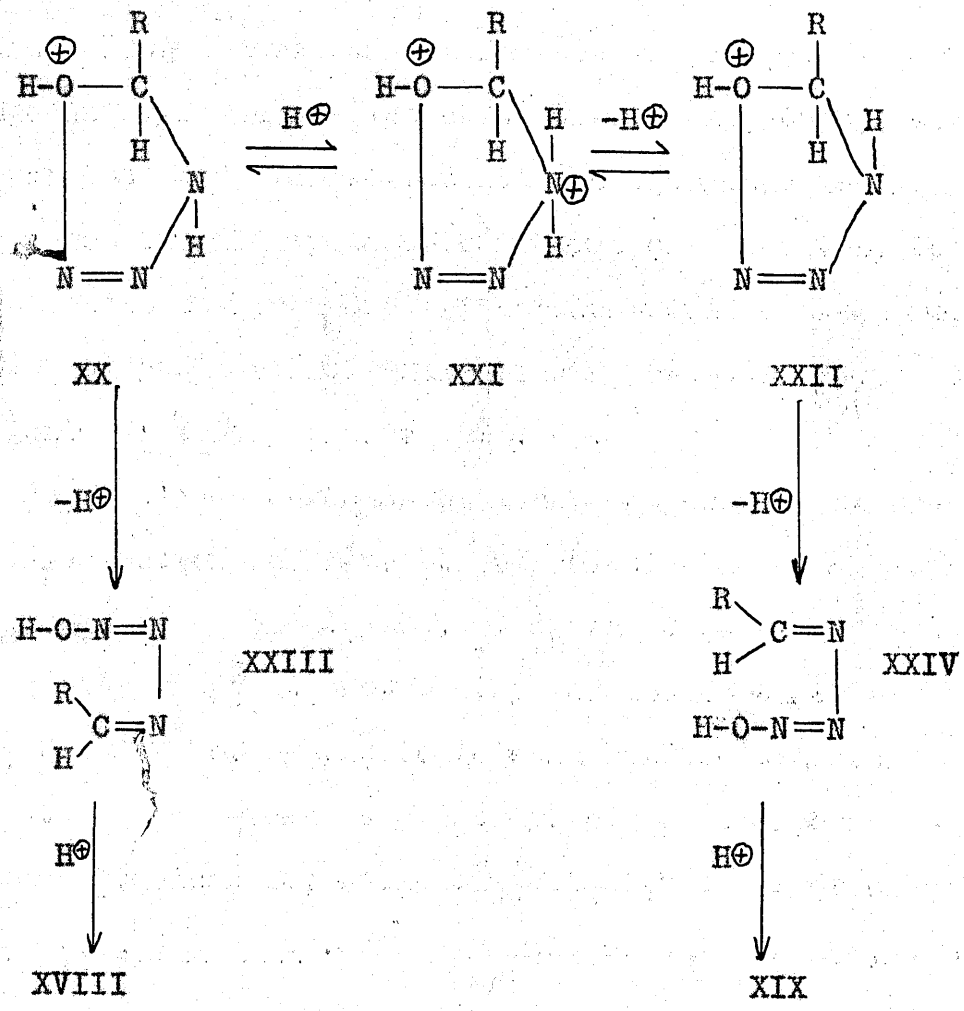
facts suggest that acceleration of nitrile formation outweighs acceleration of interconversion between XVIII and XIX where the substituent is a methoxy group; and that deceleration of interconversion between XVIII and XIX outweighs deceleration of nitrile formation where the substituent is a nitro group.

One fact inconsistent with this explanation is that the reaction of p-nitrobenzaldehyde at the high concentration of sulfuric acid is by far the fastest reaction of all ten which were studied.

In view of the isolation of the stable 5-phenyl-5,6-dihydro-1,4,2,3-oxatriazine from the reaction of styrene oxide and sodium azide, the assumption that a similar ring plays a role in the Schmidt reaction of ketones and aldehydes seems a reasonable possibility. Morton (114) made a similar suggestion without any experimental evidence. The complex XVIII could conceivably undergo ring closure to give two stereoisomeric derivatives XX and XXII (on the following page). By loss of a proton at position 4 in the ring and simultaneous cleavage of the carbon-oxygen bond, XX and XXII would give rise to XXIII and XXIV, respectively. In the presence of acids, the latter would be converted to XVIII and XIX. An alternative route of interconversion between

the two isomers XVIII and XIX might be the intermediate XXI formed by the addition of a proton to XX or XXII.

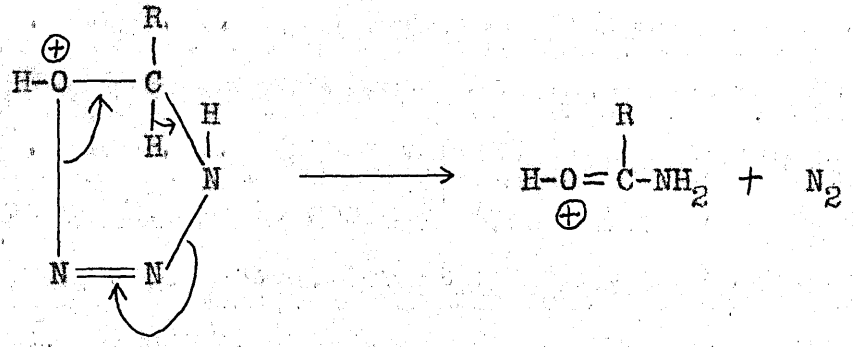
XVII



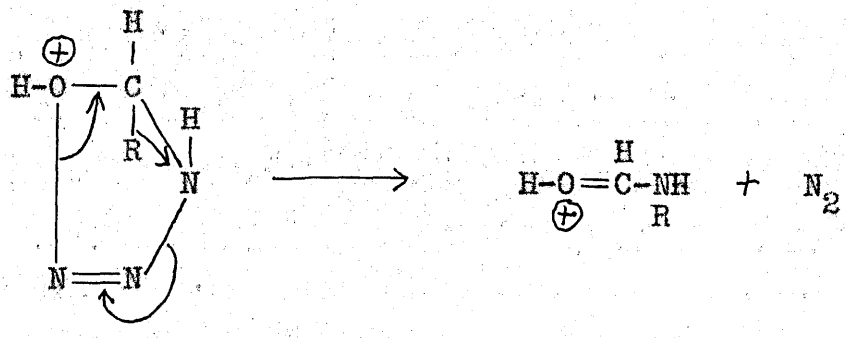
Isolation of a 5-substituted-1,4,2,3-oxatriazole would provide valuable support for a mechanism postulating such a ring. However, attempts to prepare such a ring

system by reaction of anisaldehyde and p-chloro benzaldehyde with sodium azide were unsuccessful.

An alternate mechanism for the formation of the nitrile and formanilide in these aldehyde reactions might be proposed involving 1,2-shifts within the rings XX and XXII:



XX



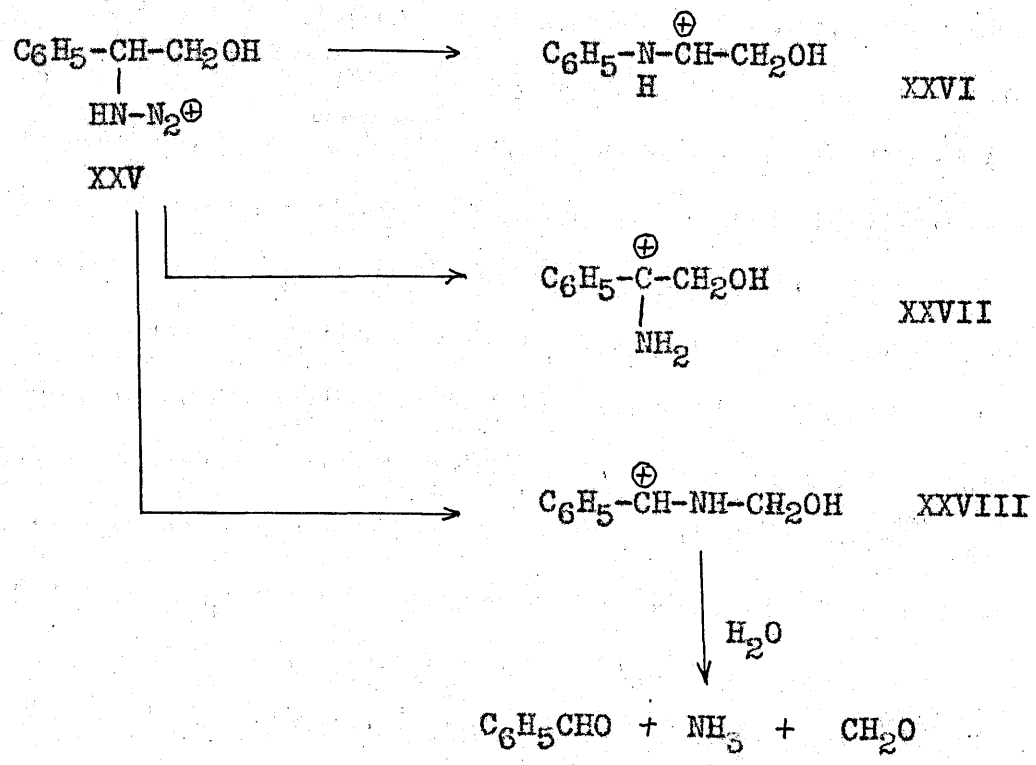
XXII

In order for this mechanism to possess at least the minimum of validity, the benzamide formed from XX would have to be dehydrated to the nitrile under the conditions of the reaction. An experiment on benzamide itself dissolved in sulfuric acid under approximately the conditions of

the reaction showed that it was recovered unchanged from the solution. Other reports in the literature (115, 116) also indicate that amides are not dehydrated to nitriles by the action of sulfuric acid. The anisamide formed in the reaction of anisaldehyde at the high concentration of sulfuric acid is thought to have resulted from the hydrolysis of the initially formed anisonitrile.

C. THE MECHANISM OF THE REACTION OF STYRENE OXIDE WITH HYDRAZOIC ACID

The yields of products isolated from the acid catalyzed reaction of styrene oxide and hydrazoic acid do not permit assignment of a mechanism. However a priori considerations suggest that the first step must be the formation of the conjugate acid of styrene oxide, which then reacts by an S_N1 mechanism with hydrazoic acid at the secondary carbon atom to give the addition complex XXV.



This could then rearrange in three different ways: 1. to form the conjugate acid of the Schiff base of aniline and glycollic aldehyde; 2. to form XXVII, the

conjugate acid of the Schiff base of phenacyl alcohol and ammonia; 3. to form XXVIII, which should hydrolyze to benzaldehyde, ammonia and formaldehyde.

A low yield of aniline, presumably formed by route 1, was the only isolable and identifiable product of any significance.

D. THE S_N2 REACTION OF STYRENE OXIDE WITH SODIUM AZIDE

The isolation of the oxatriazine from the reaction of styrene oxide with sodium azide is of significance not only as support for a cyclic intermediate in the Schmidt reaction of aldehydes and ketones, but also as a contribution to the theory of the S_N2 reactions of epoxides. The azide ion appears to have attacked exclusively at the secondary carbon atom of styrene oxide. Considering the fact that, as a linear structure of very small size, the azide ion possesses only very small steric requirements, this is in line with the results reported by other workers (73, 74, 75) on the position of attack of less bulky anions on styrene oxide. In fact it may be that the azide ion has lower steric requirements than any of the other anions yet tried, and it may give some secondary attack in unsymmetrical epoxides which heretofore have given nothing but primary attack with other reagents.

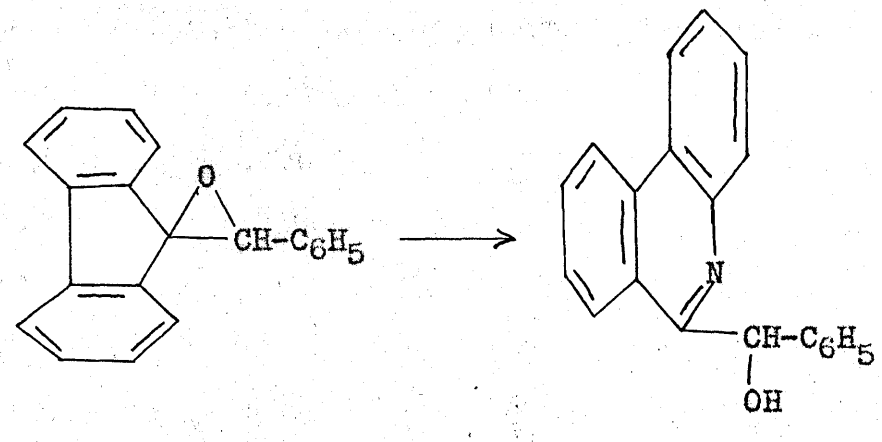
PART IV

SUGGESTIONS FOR FURTHER INVESTIGATION

The problem of further clarification of the mechanism of the reaction of aldehydes with hydrazoic acid is a difficult one. However it would be worthwhile making further attempts to isolate the dihydro-oxatriazole which has been postulated as an intermediate. Perhaps the reaction of more basic aldehydes, such as trimethylacetaldehyde, with sodium azide would give the oxatriazole where the experiments described above failed. Use of solutions of hydrazoic acid instead of sodium azide might succeed, just as it was found that some chloroimides reacted more readily with hydrazoic acid than with sodium azide.

A further study of the products of the acid catalyzed reaction of epoxides with hydrazoic acid might be fruitful. The reaction of styrene oxide and cyclohexene oxide under conditions previously used, but with a large excess of acetic anhydride in the reaction mixture, might succeed in producing identifiable products in larger yields. The use of other readily available epoxides which might give more stable and more easily isolated products also suggests itself. Thus glycidic esters might be expected to give derivatives of unsymmetrical acyloins. Some of the epoxides prepared by Bergmann and Hervey (117) should lead to quinoline deriva-

tives. Thus synthetic routes such as the following might be possible:



If the acid catalyzed reactions of epoxides fail, it may be found preferable to do the reactions in two steps. If oxatriazines are truly intermediates in the acid catalyzed reaction of epoxides with hydrazoic acid, the same products should be isolated by treating the oxatriazine itself with acid. This would permit a greater variation of conditions under which the oxatriazine is to be decomposed, and the deleterious effect of acid on the epoxide would be avoided. The benzoyl derivative of the oxatriazine might give a smoother acid catalyzed reaction than the oxatriazine itself.

The azide ion may prove to be a useful reagent in the study of the S_N2 reactions of epoxides. It would be worthwhile to study the reaction of sodium azide with other epoxides which have been reported to give

little or no attack at secondary or tertiary carbon atoms with other anionic reagents. Such epoxides are butadiene monoxide, propylene oxide, and isobutylene oxide.

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